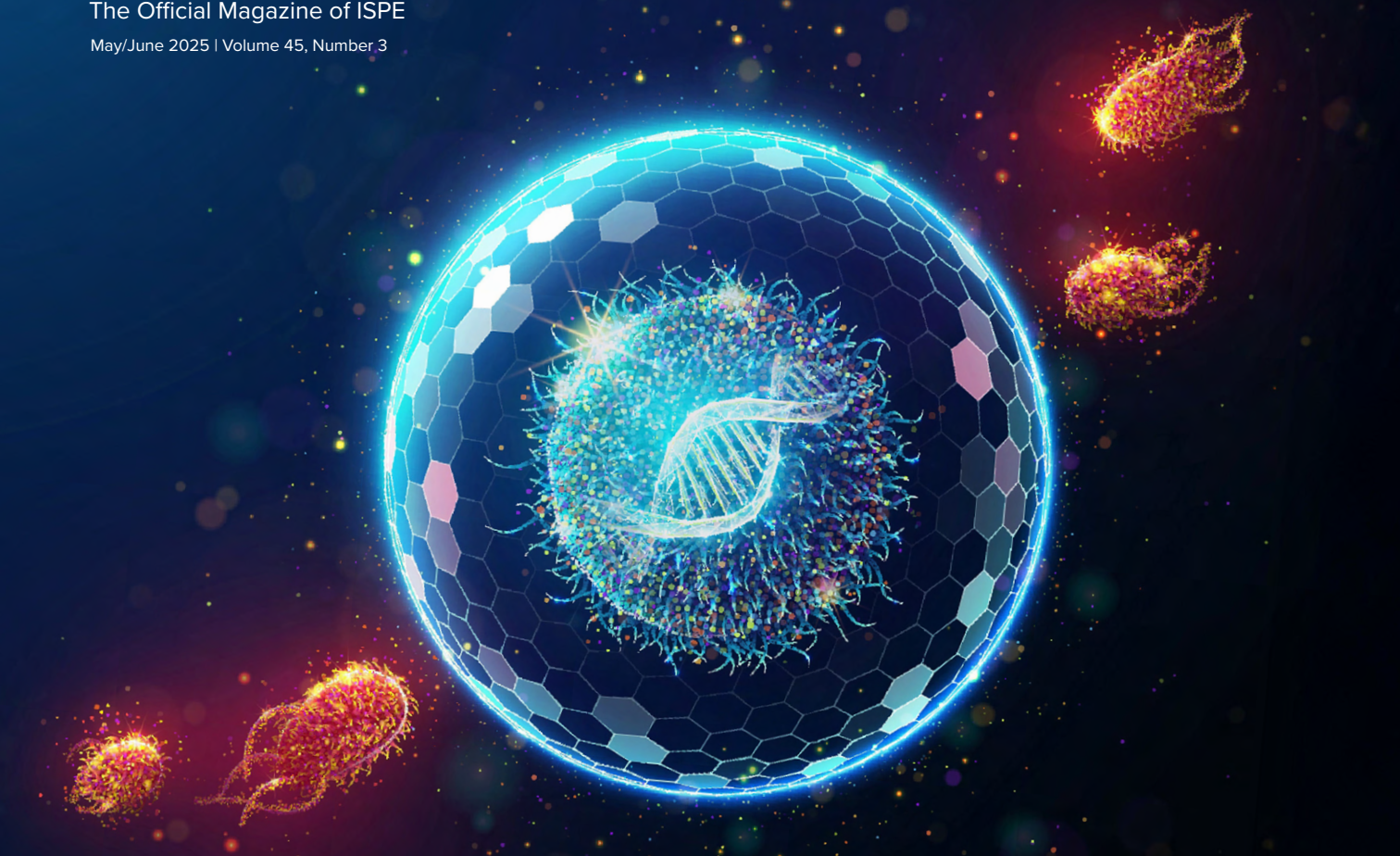
PHARMACEUTICAL ENGINEERING®

The Official Magazine of ISPE

May/June 2025 | Volume 45, Number 3



ADVANCED THERAPY MEDICINAL PRODUCTS

THE ATMP ISSUE

The Future of Automated Cell Therapy Manufacturing

Final Preparation of ATMPs at Point of Care

Unlocking ATMPs: Reducing Cost as an Obstacle to Patient Access

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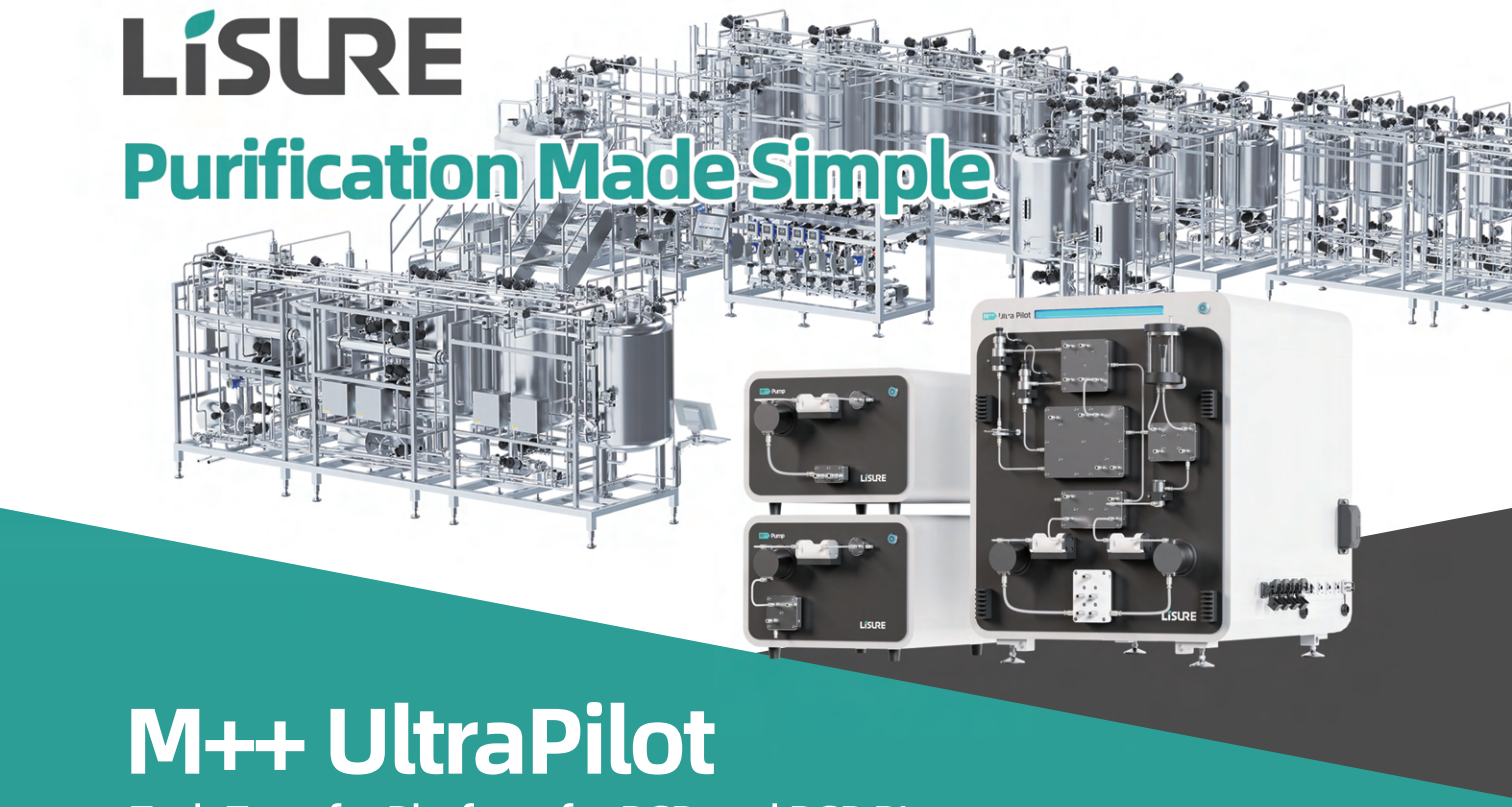

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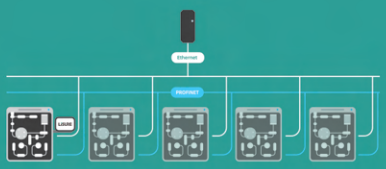

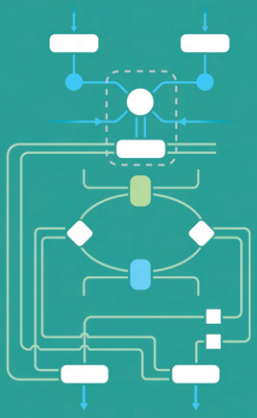

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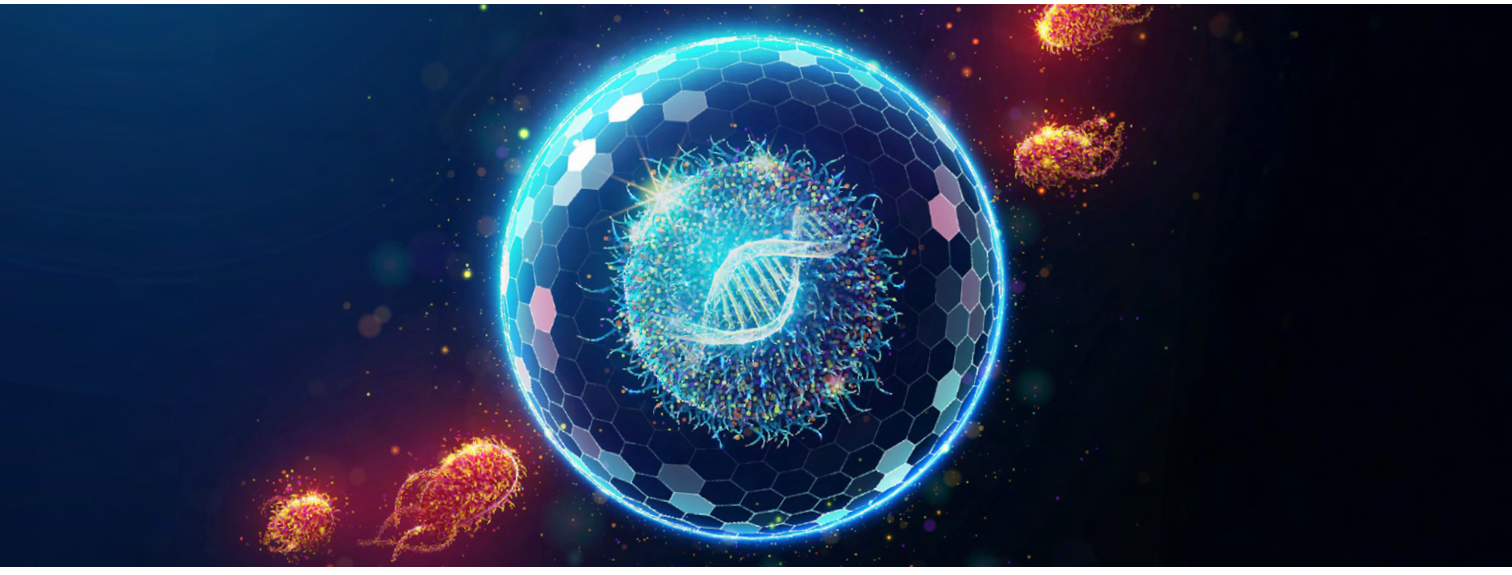

IN THIS ISSUE Advanced therapy medicinal products (ATMPs) are poised for a significant year in 2025 due to their groundbreaking potential to treat complex diseases. However, the production processes for these therapies face substantial challenges, including scalability, consistency, and the need for automation to make these treatments more widely accessible.

Integration of legacy equipment is easy

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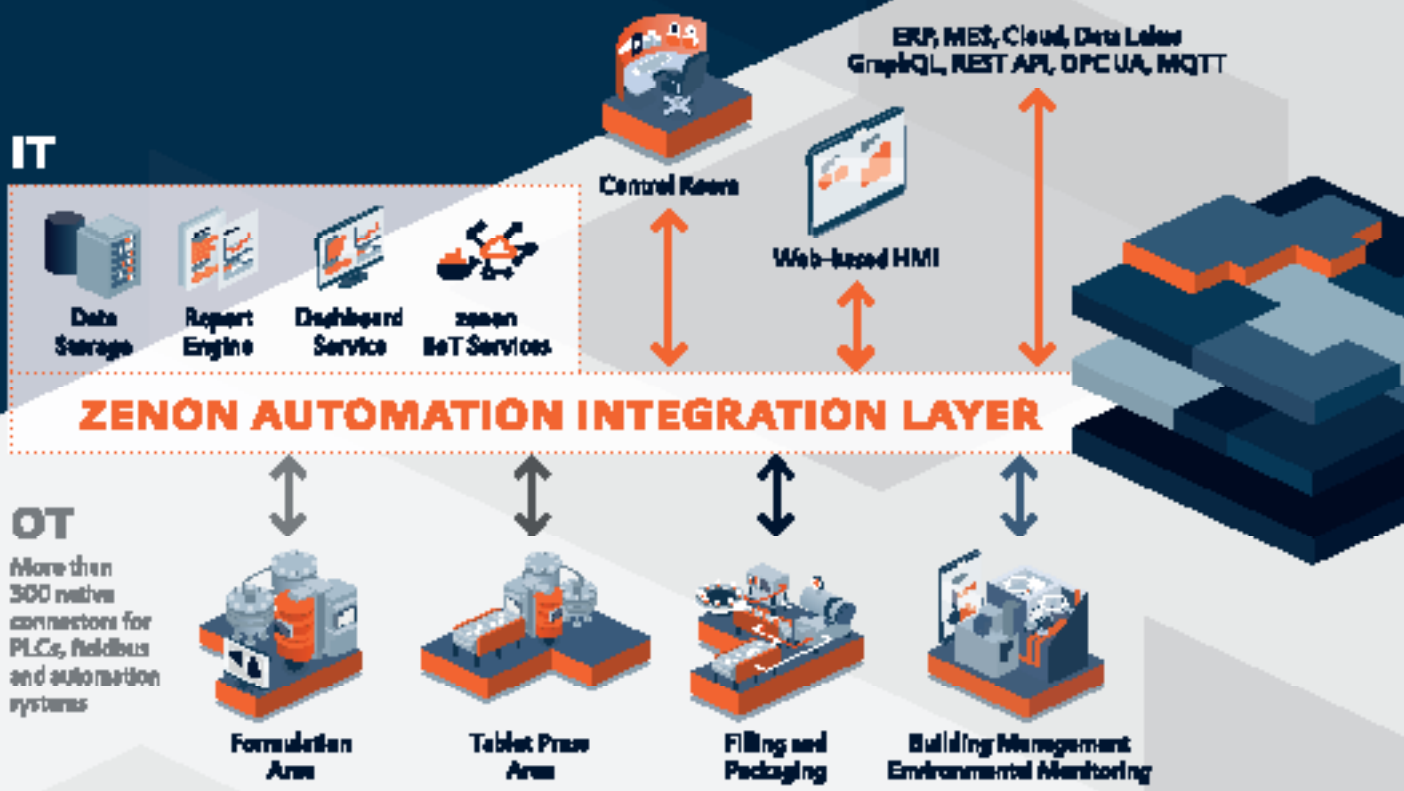

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THE ATMP ISSUE

In this issue, we focus on the manufacturing of advanced therapy medicinal products, the costs associated with patient access, and readiness.

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EDITORIALS AND COLUMNS

PEOPLE + EVENTS

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PHARMACEUTICAL ENGINEERING

Volume 45, Number 3

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

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

Printing
Sheridan NH

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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

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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:
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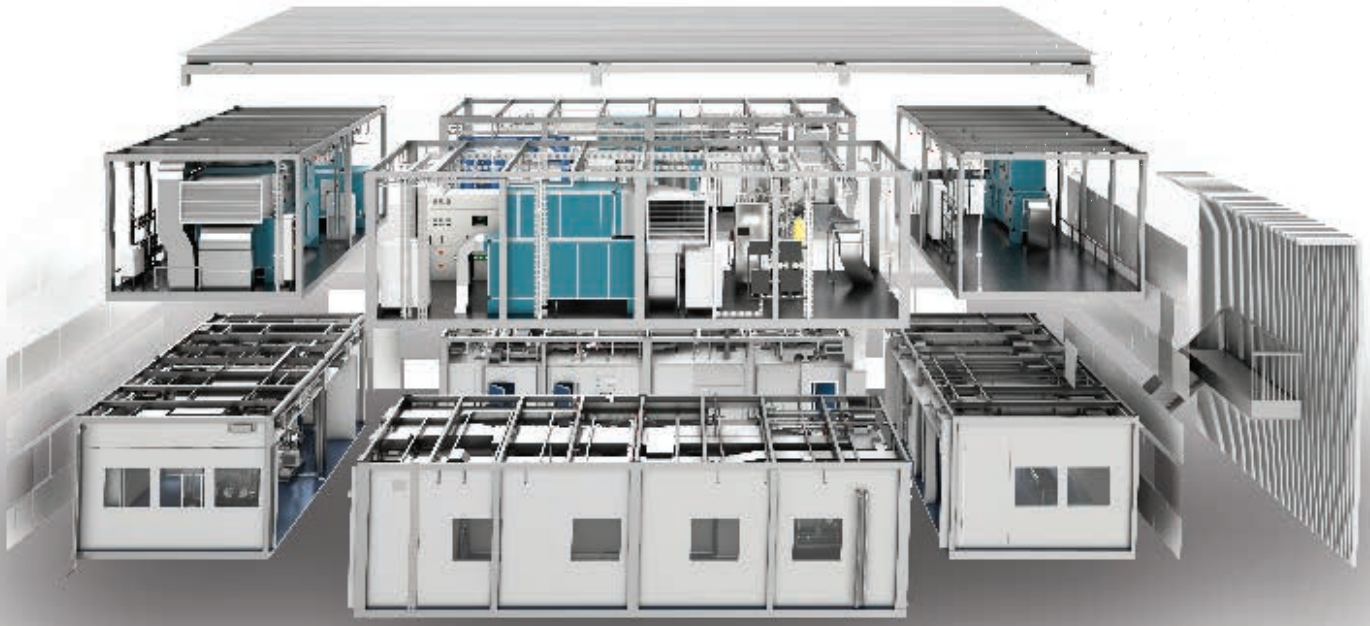

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By Jeffrey A. Biskup, PE


Jeffrey A. Biskup, PE

ISPE Guides and Resources on Biopharma, ATMPs, and C&GT

Biopharmaceuticals continue to proliferate in the pharmaceutical industry leading to advancements in advanced therapy medicinal products (ATMPs), cell and gene therapy (C&GT), and other biological products. ISPE supports its membership base of over 22,000 members across more than 120 countries by informing strategies, supporting solutions, and improving processes in this continually evolving field.

NETWORKING OPPORTUNITIES

ISPE sponsors several conferences each year. The 2025 ISPE Europe Annual Conference took place 12-14 May in London, England, UK, where industry experts and thought leaders in the pharmaceutical and biopharmaceutical industries, and global regulatory agencies met for four days. Also taking place this spring, the 2025 ISPE Biotechnology Conference, 2–3 June in Boston, Massachusetts, US. The 2025 ISPE Annual Meeting & Expo will take place 26-29 October in Charlotte, North Carolina, US. Featured speakers include John Daniel, a Human Resources Executive and author of Ancestral Mindset, a book that explores leadership and teamwork from an evolutionary-neurological perspective; Brendan O'Callaghan, Executive Vice President of Manufacturing and Supply at Sanofi; and Elaine Shannon, Global Quality Officer at Takeda.

REAL-WORLD INSIGHTS WITH ISPE GUIDANCE DOCUMENTS

ISPE has published over 80 guides with pharmaceutical industry experts who offer practical, real-world insights from industry best

practices to regulatory expectations. Guidance documents cover a wide range of topics, arming professionals with best practices and regulatory insights that meet specific needs.

BIOPHARMACEUTICAL-FOCUSED GUIDES

ISPE publishes a variety of guides for professionals in biopharmaceuticals. For example, the *ISPE Guide: Biopharmaceutical Process Development and Manufacturing* offers a universal roadmap for developing cost-effective, regulated biopharmaceutical manufacturing processes that meet their intended use in a timely manner. The Guide focuses on the development, process approaches, and best practices for manufacturing biopharmaceutical products.

The *ISPE Good Practice Guide: Development of Investigational Therapeutic Biological Products* provides a comprehensive overview of product and process development, manufacturing, investigational product supply chain management, quality control/quality assurance, and global regulatory requirements for biopharmaceuticals.

The *ISPE Baseline® Guide: Volume 6 – Biopharmaceutical Manufacturing Facilities (Third Edition)* includes key discussion points on integrating quality risk management into biopharmaceutical manufacturing to reduce risk and enhance control strategies. It also contains an in-depth analysis of contamination control strategies and their impact on facility design and operational procedures and an exploration into how closed processes influence facility design.

ATMP-FOCUSED GUIDES

ATMPs are a fast-growing field of interest in the pharmaceutical industry, with many ATMPs in development and continual growth projected. ATMP therapies include gene therapies, somatic-cell therapy, and tissue-engineered medicines, for example. ISPE ATMP-related guides cover allogeneic cell therapy, autologous cell therapy, and recombinant adeno-associated virus manufacturing (rAAV) manufacturing and comparability.

The *ISPE Guide: Advanced Therapy Medicinal Products – Allogeneic Cell Therapy* focuses on the development and design of manufacturing facilities for these therapies. It provides answers to common challenges faced in allogeneic cell therapy facilities, explores design concepts tailored for these facilities, and presents valuable insights into GMP layout and architectural design development.

The *ISPE Guide: Advanced Therapy Medicinal Products – Autologous Cell Therapy* primarily focuses on the development and design of manufacturing facilities for autologous cell therapies for parenteral use. The Guide offers an in-depth overview of the key components necessary for designing ATMP facilities. It also explains how unique characteristics and requirements of the manufacturing process and the facility must be specifically aligned for ATMPs.

The *ISPE Guide: Advanced Therapy Medicinal Products – Recombinant AAV Comparability and Lifecycle Management* outlines best practices for rAAV comparability exercises, equipping manufacturers with a standardized approach for developing process and product comparability strategies.

PROFESSIONAL DEVELOPMENT TRAINING

From an overview of biopharmaceutical manufacturing processes to ATMP manufacturing, ISPE offers a range of professional development training opportunities for both newer and seasoned professionals. For more information about these and other benefits of an ISPE membership, email ask@ISPE.org

Jeffrey A. Biskup, PE, is the Executive Chairman of the Board at CRB and the 2024–2025 ISPE International Board Chair. He has been an ISPE member since 1998.

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By Miriam Kremer-van der Kamp


Miriam Kremer-van der Kamp

WORKFORCE OF THE FUTURE: WOMEN IN PHARMA® AT THE 2025 ISPE EUROPE ANNUAL CONFERENCE

Each year, the ISPE Europe Annual Conference includes a dedicated Women in Pharma® session, providing an open and collaborative space on professional and personal development. The session fosters meaningful discussions, mentorship, and knowledge-sharing to empower individuals and drive positive change within the industry.

This year's conference, which was 12-14 May in London, UK, included the session, "Workforce of the Future – Challenges and Opportunities." Led by the Woman in Pharma® United Kingdom (UK) Affiliate, it explored the shifting dynamics in workforce transformation driven by diversity, innovation, and adaptability. Attendees gained a deeper understanding of these trends and how they may impact the industry.

PREPARING FOR WORKFORCE TRANSFORMATION

The pharmaceutical industry is undergoing rapid transformation, driven by advancements in digital technology, shifting workforce expectations, and evolving industry demands. As companies navigate these changes, they must adopt proactive strategies to ensure their workforce remains adaptable, skilled, and prepared for the future. This session explored how organizations can respond to transformation.

One area of discussion focused on generational workforce trends. It analyzed how people of different generations offer unique perspectives, strengths, and challenges to the industry. Understanding these dynamics is crucial to developing effective talent management strategies. Another theme was diversity and inclusion, moving beyond regulatory compliance to cultivate workplaces that harness the benefits of diverse teams and foster innovation through inclusive leadership.

The session explored the increasing role of digitalization in reshaping pharmaceutical operations. Automation, artificial intelligence, and digital tools are transforming the skills required for industry professionals, making it essential to invest in continuous learning and workforce upskilling. In addition, there was an in-depth discussion on the importance of soft skills, highlighting why leadership, adaptability, and collaboration are just as vital as technical expertise in ensuring long-term success in a rapidly evolving industry.

The interactive session included live polling and open discussions, ensuring attendees gained practical insights that can be applied across organizations.

COLLABORATIONS AND INITIATIVES SUPPORTING WORKFORCE DEVELOPMENT

Beyond the ISPE Europe Annual Conference, Women in Pharma® is actively involved in initiatives to support professional growth, diversity, and leadership development.

ISPE UK Summer Conference

The 2025 ISPE UK Summer Conference will take place 18 June at the National Motorcycle Museum in Solihull, West Midlands, England. While the ISPE Europe Annual Conference focuses on broad industry discussions, the ISPE UK Summer Conference will offer a more hands-on, practical approach. Emerging Leaders from the ISPE UK Affiliate have been involved with planning the event, which will explore strategies for career development tailored for early- and mid-career professionals.

The conference will provide valuable insights into the evolving skillsets that are essential for workforce adaptability. This is crucial for staying agile in an ever-changing environment. Plus, it's an opportunity to network. Attendees will have opportunities to connect with experienced industry leaders and emerging talent, creating a platform for mentorship and collaboration. By bringing together established experts and fresh perspectives, the event aims to reinforce innovative and forward-thinking workforce strategies.

Soft Skills Development for Young Professionals

Recognizing the growing importance of interpersonal and leadership skills in the pharmaceutical industry, Women in Pharma® will be hosting a two-day in-person soft-skills workshop in early September for ISPE Emerging Leaders in the UK. The workshop is designed to equip young professionals with key competencies needed to navigate a complex and highly regulated industry. Participants will have the opportunity to develop essential skills

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By Rebecca Roscher

GAMIFICATION

Re-Igniting Curiosity as Key to Life-Long Learning

In pharmaceutical manufacturing, it is crucial that we commit to lifelong learning and stay informed about the latest advancements in the advanced therapy medicinal products (ATMP) market. Staying up to date on the latest technologies and methodologies allows us to maintain a competitive edge in the industry. However, when learning becomes a "duty," we risk feeling drained of energy and becoming tired of it. Is there any way to regularly re-ignite the fun and our curiosity to remain engaged and motivated?

I recently stumbled upon my old training material from when I was a trainer at my previous job. Instructors and trainers were strongly advised to adapt their teaching methods to suit the learning styles of the next generation. Gamification has proven its worth with Generations Z and Alpha, so we were encouraged to use it. However, the value of gamification is not just restricted to younger generations. Who hasn't learned something by doing crossword puzzles in journals or newspapers, during a TV quiz show, when using an app, or just by fact-checking statements on Google?

With that, I invite you to take part in this small field test. Feel free to test your knowledge on developments in ATMPs with this quiz.

QUIZ: RISES, FAILURES, AND CHANGES IN THE GLOBAL ATMP MARKET

1. **Which statement is correct?**
   a. There are six US Food and Drug Administration (FDA)-approved ATMPs for multiple myeloma that target CD19.
   b. As of March 6, the US FDA has approved 44 cellular and gene therapy products.
   c. There are currently more than 20 ATMPs approved in Japan.
   d. Anti-infective indications are the top targeted therapeutic area by RNA therapies in 2024.

2. **Which of the following gene therapy products are approved in the EU?**
   a. Fidanacogene elaparvovec (Beqvez, previously Durveqtix)
   b. Onasemnogene abeparvovec (Zolgensma)
   c. Eladocagene exuparvovec-tneq suspension (Kebilidi in the US or Upstaza in the EU)
   d. Exagamglogene autotemcel (Casgevy)

3. **Which region is expected to have the highest ATMP market growth in 2024?**
   a. Europe
   b. Asia-Pacific
   c. North America
   d. Latin America

4. **Which company expanded its ATMP pipeline in 2024-25 without an acquisition?**
   a. AstraZeneca
   b. Roche
   c. Pfizer
   d. Kyowa Kirin

5. **How many developers are in the ATMP sector?**
   a. 2,900
   b. 3,400
   c. 4,100
   d. 4,800

6. **Which regulatory agency published a revised roadmap for the regulatory framework of medical devices in December 2024?**
   a. Japan Pharmaceuticals and Medical Devices Agency (PMDA)
   b. UK Medicines and Healthcare Products Regulatory Agency (MHRA)
   c. Health Canada
   d. South Korea Ministry of Food and Drug Safety (MFDS)

7. **Which of these ATMPs were not discontinued after approval?**
   a. Glybera
   b. Zalmoxis
   c. ChondroCelect
   d. Lifileucel

8. **In what areas are clinical trials in Europe declining?**
   a. Oncology
   b. Neurology
   c. Rare disease
   d. Immunization
   e. Pediatric conditions

9. **There are more gene therapy trials in oncology than for any other condition?**
   a. True
   b. False

10. **Which of the following statements are false?**
    a. Phase 1 clinical trials for ATMPs almost doubled in the UK from 2023 to 2024.
    b. In Sweden, there has been a strong increase in CAR T cell treatments for the last three years.
    c. Front-runners in active ATMP clinical trials include Celgene and Mesoblast.
    d. China conducts the most CAR T cell treatments globally.

See answers on page 82.


Lou Schmukler

LESSONS FROM THE EMPOWERMENT BATTLEFIELD

Empowerment is providing employees with the autonomy, tools, and trust to make decisions that impact their roles and the organization. It requires a shift from the more traditional directive or micromanagement style to fostering a sense of ownership and accountability.

During the late 1980s, I was working for a fast-growing, mid-sized pharmaceutical company in the US Midwest. I was a young, inexperienced manager at the time, still learning the principles of good leadership. The head of manufacturing, with an ambition to create a world-class manufacturing organization, decided that self-directed work teams (a strategy originally developed in Britain following World War II to enhance economic productivity) was one of the key strategies to accomplish this objective.

There was soon a small army of expert consultants engaged to advise and guide us on this journey. I was fortunate to be selected as a member of the initiative's design team. The team was tasked with the Herculean job of developing a new organizational model and an implementation plan. This would be my first experience with a major workforce empowerment and culture change agenda. It would prove to be an experience I would leverage for the next 35 years of my career.

WORKFORCE EMPOWERMENT

I'll pause my story here for a brief overview of workforce empowerment. Simply put, empowerment is providing employees with the autonomy, tools, and trust to make decisions that impact their roles and the organization. It requires a shift from the more traditional directive or micromanagement style to fostering a sense of ownership and accountability. The essential factors of empowerment include:

- Building trust
- Establishing clear goals, guidelines, and expectations
- Investing in coaching, development, and new skills
- Ensuring strong communication and feedback loops
- Providing flexibility in work arrangements
- Ensuring effective recognition and incentives

OUTCOMES

The desired outcomes of empowerment is a workforce that is more motivated, inspired, and confident. It is a workforce that trusts its leadership, has greater creativity, and makes a bigger impact on the company's bottom line. A study of over 7,000 employees who did not feel empowered rated at the 24th percentile of engagement, whereas those with a high level of empowerment came in at the 79th percentile [1]. This major difference highlights the impact of empowerment on engagement.

A recent survey showed engagement driven by empowerment significantly improved several key operating indicators. These included employee satisfaction, quality, safety, absenteeism, productivity, and profitability. The organizational strategy of self-directed work teams mentioned before raises the concept of empowerment to its highest level. For years, advocates of this strategy have promoted its benefits of added flexibility, better problem-solving skills, and greater productivity.

IMPLEMENTATION

Our team took a "top down, bottom up" approach, starting with meeting key stakeholder groups and listening carefully to their input. Some groups were excited and optimistic, whereas others were concerned and pessimistic about the probability of success. There were no unexpected responses for a major change effort. After months of work, management endorsed our plan and began implementation. The plan was both complex and comprehensive. The central elements involved:

- Substantial delayering of the organization with a redefinition of supervision and management roles
- End-to-end process work team structure
- An extensive training program aligned with a new pay-for-skills compensation system
- Broader information sharing with new performance metrics
- Major delegation of responsibility, accountability, and decision making-to the teams (the plan we developed was very ambitious, and we eventually discovered it was too ambitious)

The failure rate for this type of change effort is high. Finding the right balance between autonomy and control is not easy. And of course, there's always the inherent resistance to change and desire to maintain the status quo. Unfortunately, our project

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CONTINUED FROM PAGE 8, "WOMEN IN PHARMA®"

such as effective communication, teamwork, and leadership. The workshop will also provide mentorship opportunities with seasoned industry professionals who can offer guidance and career insights. By fostering these critical skills, the program aims to support the next generation of industry leaders in building successful and sustainable careers.

Embracing Diversity in the Workplace

The ISPE UK Affiliate and Women in Pharma® collaborated with the Chartered Institute of Building to develop a five-part webinar series focused on neurodivergence and underrepresented talent in the built environment and life sciences industries. These sessions will explore barriers to workplace inclusion and identify strategies for fostering more inclusive environments. The overwhelming response from participants highlights the need for continued discussions and employer-driven initiatives to create lasting change.

An in-person session is planned for November 2025 at the ISPE UK Affiliate Annual Conference in Manchester, England. This session will allow for deeper engagement offering participants a chance to share best practices, exchange insights, and explore actionable steps toward greater workplace inclusivity.

Shaping a Resilient and Inclusive Workforce

Beyond the ISPE Europe Annual Conference, Women in Pharma® UK continues to play a vital role in supporting workforce development, leadership growth, and industrywide collaboration. Efforts such as regional professional development workshops, networking events, and strategic partnerships are just a few examples of how Women in Pharma® UK fosters a more inclusive and resilient workforce while strengthening connections across the pharmaceutical sector. These UK-driven initiatives create meaningful impact at a regional level while aligning with our larger global movement.

HOW TO GET INVOLVED

Women in Pharma® is dedicated to fostering an inclusive and supportive environment in the pharmaceutical industry. By bridging gender, cultural, and organizational gaps, Women in Pharma® empowers professionals through mentorship, knowledge-sharing, and leadership development. Our initiatives aim to create a more equitable and diverse industry, where individuals can grow personally and professionally.

We encourage everyone to get involved. Share your experiences, and contribute to shaping the future of the industry. Whether it's through mentorship, events, or networking, there are many opportunities to be part of this dynamic community. Let's work together to build a future-ready workforce. Visit us online at ispe.org/women-pharma

Miriam Kremer-van der Kamp is a dedicated business development professional with a background in operations, project management, and process engineering within the pharmaceutical and biopharmaceutical industries. She is the Emerging Leader Liaison of the Women in Pharma® International Steering Committee. She joined ISPE in 2022.

CONTINUED FROM PAGE 10, "EMPOWERMENT BATTLEFIELD"

would end up being one of the failures, not one of the successes.

LESSONS LEARNED

The after-action report identified numerous reasons for the failure, but these could be distilled down to just four central mistakes. First, there was a lack of clear leadership because of front-line supervision and middle management confusion over the new roles. (What does it mean to be a coach and facilitator vs. a more traditional supervisor and manager?) Second, there was internal and external sabotage to the teams. Some managers just gave lip service to the effort and went on doing things as they always had. There were team members who didn't want to take on the added accountability and responsibility because of fear, or not wanting the burden of too much additional work.

Third, it was difficult within the teams to hold people accountable, and conflicts and power struggles arose. And finally, one of the business cases for self-directed teams is the economics. This involves doing more with less, including labor. This was a difficult challenge for the teams to handle because it meant fewer staff working more. As a result of these issues, operational performance progressively declined, and management was ultimately forced to abandon the project after a lot of time and money spent.

Not all strategies are successful. Sometimes these strategies provide the most valuable lessons. In this case, the manufacturing organization learned from the failure, applied those learnings, bounced back quickly, and went on to do bigger and better things. As for me, I took away some valuable leadership lessons.

First, one size doesn't fit all. Although we had visited several companies with successful implementations, this strategy was not right for our culture. Second, in any change initiative there will be people who are just not on board and never will be. It's vital to quickly identify them and take decisive action. If you don't, they will be a detriment to the organization going forward. Third, good management is good management regardless of the circumstances. Whether organized in self-directed teams or a traditional hierarchy, clarity of direction, coaching, and development are always essential. There's no substitute. In this experience, I've learned more from failure than success. "The only real mistake is the one from which we learn nothing," said Henry Ford.

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Lou Schmukler, MA, served as Executive Vice President and President of Global Product Development and Supply at Bristol Myers Squibb until his retirement. His pharmaceutical industry career spanned over 40 years. He joined ISPE in 1993.

STREAMLINING THE VEIN-TO-VEIN PROCESS:

The Future of Automated Cell Therapy Manufacturing

By Krisha Patel, Judith Koliwer, PhD, and Kruti Shah

Cell therapies, especially autologous chimeric antigen receptor T cell (CAR T cell) treatments, are transforming personalized medicine, bringing new hope to patients with conditions once thought untreatable. However, the manufacturing processes for these therapies remain predominantly manual, presenting significant challenges in scalability, consistency, and making these treatments more widely available.

Manual manufacturing processes are labor-intensive and time-consuming, often involving up to 50 manual steps per dose and requiring approximately 80 hours of labor [1, 2]. This complexity not only increases the risk of human error and contamination but also contributes to substantial production costs, with labor accounting for nearly half of the total manufacturing expenses [1, 2].

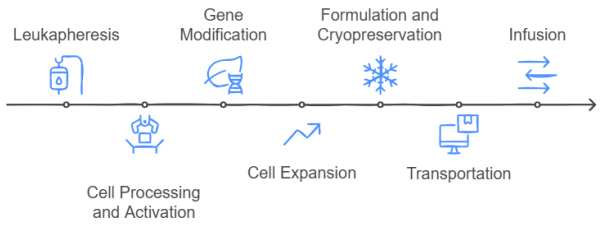
The stakes in cell therapy manufacturing are incredibly high. Lengthy production times not only delay treatment but, in some cases, have devastating consequences. Reports indicate that approximately 20% of patients die while waiting for CAR T cell therapy so there is an urgent need for more efficient processes [3]. Research analyzing the impact of reducing waiting times from 1 to 9 months to zero using a health system-level discrete event simulation model suggests that reducing wait times by just two months could improve treatment efficacy by as much as 14%, offering hope for better patient outcomes [4].

To tackle these challenges, the industry is rapidly embracing automated and closed manufacturing systems that promise to enhance reproducibility and reduce labor costs through optimized processes. This will open doors for cell and gene therapies to move from niche treatments to first-line options, considering other solutions related to control over side effects. The integration of automated manufacturing, automated data collection, and advanced analytics is not just a step forward, it is important to overcome current manufacturing bottlenecks and enhancing process understanding. This article will provide insights into what a fully automated manufacturing process looks like, the type of data collected, how advanced data analytics tools can support process understanding, and special considerations for validating a fully automated manufacturing platform.

AUTOMATED CAR T CELL THERAPY MANUFACTURING PLATFORM

The journey of CAR T cell therapy, from extracting a patient's cells to delivering a life-saving treatment, is often referred to as the "vein-to-vein" process. This personalized therapy has immense potential, but the complexity, variability, and cost

Figure 1: **Automated CAR T cell manufacturing platform process.**



of manufacturing present significant hurdles. Automation is revolutionizing this process, streamlining each step to enhance efficiency, ensure consistency, and accelerate delivery. The vein-to-vein process in CAR T cell manufacturing involves several critical stages, each improved by automation.

The process begins with leukapheresis, where automated machines ensure precise collection and separation of T cells and digital systems standardize protocols to minimize errors. During cell processing and activation, closed systems and robotic tools handle cell washing, concentration, and reagent addition, reducing contamination risks. In the gene modification step, automated platforms deliver genetic material consistently, with sensors monitoring conditions in real time. For cell expansion, closed bioreactors equipped with sensors and automated media exchange systems support optimal growth.

During formulation and cryopreservation, robotics ensure accurate dosing and controlled freezing for safe storage. Automation also supports transportation and chain of custody with real-time tracking and secure data systems like blockchain to maintain integrity. Finally, at infusion, though less automated, digital tools ensure seamless data transfer to clinicians for patient care. Automation across these stages improves efficiency, consistency, and safety in CAR T cell manufacturing.

PLATFORM DESIGN FOR AUTOMATED CAR T CELL MANUFACTURING

The automated manufacturing platform is designed with modular workstations that seamlessly handle the entire process, from leukapheresis to cell expansion and final infusion. Each workstation integrates specialized automated instruments—including cell separators, bioreactors, and cryopreservation units—to streamline and standardize the workflow. Instruments are interconnected through a centralized software system that orchestrates the entire process. This system manages workflows, tracks patient-specific samples, and provides real-time data monitoring.

By linking all components, the platform reduces manual intervention, minimizes errors, increases efficiency, and ensures compliance with strict regulatory requirements. Advanced sensors and analytics tools are embedded within the platform to monitor critical parameters such as temperature, pH, and cell viability at every stage. This real-time monitoring ensures optimal conditions are maintained, enhancing product quality and consistency.

AUTOMATED DATA COLLECTION FOR ADVANCING CELLULAR THERAPY MANUFACTURING PROCESSES

As the advanced therapy medicinal products (ATMPs) industry matures, the need for a standardized approach for process characterization becomes more apparent. Lack of process characterization can lead to risk of batch failure, higher costs, and impaired quality, which are especially critical in personalized ATMP products. Process characterization is paramount to tech transfer, e.g., between sponsor and contract development and manufacturing organizations (CDMOs) or different facilities.

Reports indicate that approximately 20% of patients die while waiting for CAR T cell therapy so there is an urgent need for more efficient processes.

The nature of personalized ATMPs has long been suggested to be ideal for decentralized manufacturing, which requires a mature, well-characterized process.

The complexity of ATMP processes, with many intervention steps and interdependent process parameters, requires solutions for process control and final product testing. Furthermore, the necessity for manual processes can lead to operational inefficiency. The inefficiencies increase as the process and individual steps are more disconnected. The vein-to-vein process in personalized ATMPs includes not only the actual manufacturing process as in more traditional pharmaceutical and biotechnology manufacturing, but this process starts and ends at the treatment center so it includes logistics and transport to and from the manufacturing site.

Compared to a classic biotechnology process, ATMP manufacturers are facing a multi-step process with additional stakeholders. Moreover, the vast majority of manufacturing processes as of today include equipment with various levels of integration and/or automation capabilities. Although the development of equipment that covers a larger part of the manufacturing process has significantly improved in recent years, the industry currently displays a mixture of automation and manual processes with different levels of automation, but always containing manual intervention and data collection. Even the most mature automation equipment requires manual intervention, e.g., in process analytics and activities at the treatment center.

Another level of diversity in the process is the equipment itself. Although recent developments have reinforced the integration of equipment by providing standard interface capabilities like open platform communications (OPC), many industry-standard devices still lack integration capabilities. This situation leads to disconnected processes and data silos, resulting in data that cannot be used over different process steps for process characterization, as well as a lack of data availability for digital solutions. Moreover, the strict requirements for traceability and process monitoring cannot be compromised, which leads to additional effort to ensure that all requirements are met.

By utilizing advanced instrumentation and continuous monitoring systems, manufacturers can gather high-resolution data in real time across critical stages of production.

Automated data collection is essential for modernizing cell therapy manufacturing. By utilizing advanced instrumentation and continuous monitoring systems, manufacturers can gather high-resolution data in real time across critical stages of production. This data provides valuable insights into cell behavior, enabling tighter control of manufacturing processes and enhancing product quality. Crucial data sources include:

- Flow cytometers: These instruments enable high-throughput characterization of cellular populations by surface marker expression. This capability is crucial for ensuring product identity, potency, and consistency.
- Real-time cell analyzers: These systems allow continuous monitoring of cell growth, viability, and morphological changes, enabling prompt adjustments to culture conditions.
- Next-generation sequencing (NGS): These platforms provide comprehensive insights into genetic modifications and integrity, aiding in the validation of gene-edited or transduced cell products.
- Bioreactors: These automated devices offer data on crucial parameters (cell density, nutrient consumption, and metabolite production), promoting a more controlled expansion environment.

TYPES OF DATA AND PARAMETERS NECESSARY FOR PROCESS CONTROL

To effectively integrate data analytics into cell therapy manufacturing, it is vital to identify the relevant data types and parameters that drive process control. These include:

- Cell phenotype data: Detailed information on surface marker expression, crucial for verifying cellular identity and ensuring product consistency.
- Viability and growth metrics: Continuous monitoring of cell expansion and health ensures optimal culture conditions and product yield.
- Genetic and metabolic data: NGS and metabolic profiling enable confirmation of genetic integrity and optimization of nutrient availability, respectively.

In addition to these core systems, emerging technologies further enhance data collection and analytics. Collectively, these technologies enhance manufacturing oversight by delivering near-real-time insights on cellular metabolism, viability, and genetic status. Commonly tracked parameters include cell density, nutrient levels (e.g., glucose, amino acids), metabolic byproducts (e.g., lactate, ammonia), and surface marker expression. Together, this data guides process adjustments and maintains product quality.

Live Cell Imaging and Analysis

Platforms like CytoSMART and those from Nexcelom Bioscience and IPRASENSE enable real-time monitoring of cell behavior, morphology, and viability. Halo Labs and LumaCyte provide fluorescence microscopy and label-free sorting for enhanced quality assessment.

Flow Cytometry and Phenotypic Analysis

Accellix offers cartridge-based solutions for streamlined phenotypic analysis, and Progen Biotechnik provides lateral flow tests for detecting adeno-associated virus (AAV) capsids.

Genetic, Protein, and Metabolic Characterization

NanoTemper Technologies facilitates multiparameter protein and virus assessment, Parse Biosciences enables single-cell transcriptomics, and DiaMonTech offers real-time glucose monitoring via mid-infrared sensors.

Advanced Analysis and Screening Tools

Myriade Lab and Refeyn specialize in interferometric microscopy for nanoparticle analysis, Sphere Fluidics leverages picodroplet technology for high-throughput single-cell screening, and Megadalton Solutions employs charge detection mass spectrometry for biomolecule characterization.

Integrated Process Monitoring and Control

Unchained Labs and PendoTECH provide versatile tools for cell and gene therapy preparation, real-time process monitoring, and data collection to streamline manufacturing workflows.

CRITICAL PROCESS PARAMETERS (CPPs) AND CRITICAL QUALITY ATTRIBUTES (CQAs)

Establishing well-defined CPPs and CQAs is essential for achieving reproducible and high-quality cell therapy products: CPPs include environmental factors (temperature, pH, and agitation speed in bioreactors) and transfection or transduction efficiency in gene-modified therapies. CQAs include potency, identity, and purity of the final product and safety indicators, including sterility and absence of process-related contaminants. Careful monitoring and control of these parameters and attributes directly influence therapeutic efficacy, patient safety, and regulatory compliance.

INTEGRATION OF ADVANCED ANALYTICAL AND SUPPORT TOOLS

Advanced analytical tools offer opportunities to refine process monitoring and decision-making. High-content imaging systems provide detailed morphological data that informs on cell health and phenotype. Mass spectrometry enables in-depth proteomic and metabolomic studies, supporting the optimization of growth conditions. Automated liquid handlers standardize sample handling and increase throughput, mitigating variability from

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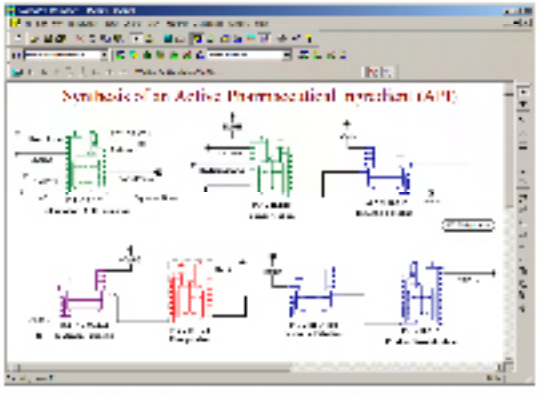

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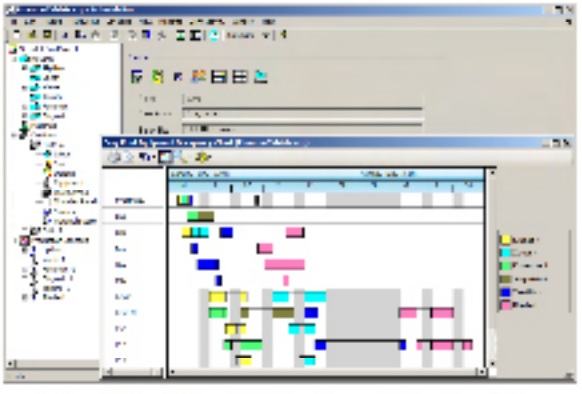
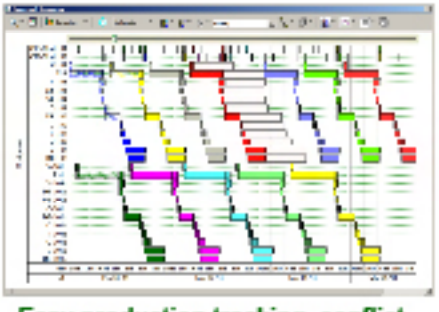
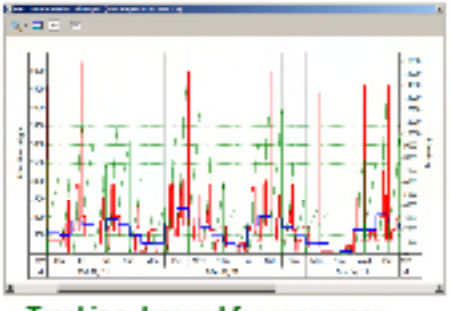


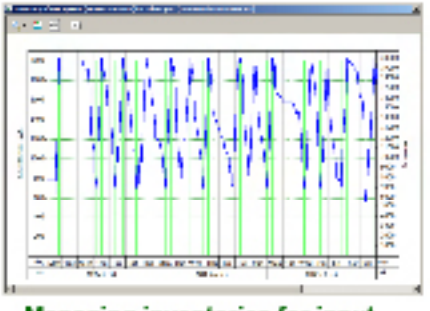
Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



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.

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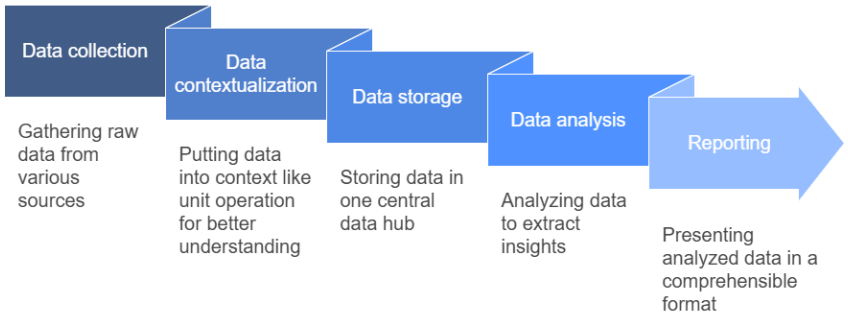
Figure 2: Flowchart of data steps supported by automation [5].



manual processes. By merging these analytical capabilities with automated data collection, manufacturers can maintain tighter control of the production process.

AUTOMATED DATA ANALYTICS

Automated manufacturing systems equipped with robust data analytics present a transformative approach to addressing current limitations in cell therapy production. Inline and online monitoring of continuous real-time data allows rapid response to process deviations, reducing manual interventions and associated error. Machine learning algorithms and AI-based models can detect patterns, predict performance outcomes, and recommend process optimizations. Automated, advanced bioreactor systems dynamically adjust culture conditions to minimize batch-to-batch variability. Such integrative solutions not only foster consistency but also expedite scale-up efforts, making cell therapies more broadly accessible.

To approach process characterization in such a complex environment, digital ecosystems should be optimized for the specifics in personalized ATMPs. Most ATMP manufacturers use an ecosystem of enterprise resource planning (ERP), patient orchestration, a manufacturing execution system (MES)/electronic batch records (EBRs), and a laboratory information management system (LIMS). However, to support the complex data flow as efficiently as possible, it is useful to optimize the data flow as early in the product life cycle as preclinical or the start of clinical trials.

An optimized data flow and data management concept can drastically speed up the process development, as the data can be used in a more powerful system. Because most manufacturers do not currently have a complete ecosystem in place, the data management concept can be developed on a hybrid ecosystem of manual and digital data and then optimized with the implementation of additional software. The data management concept should be based on process orchestration, including the process orchestration concept, mapping and coordination of the data flow, scheduling components, patient traceability, and equipment coordination.

A central system should oversee the complete process. This central system can be a manually managed spreadsheet—an MES/EBR or a process control system (PCS) system. The centralized system should be optimized for the selected equipment for first implementation, taking any future changes into consideration, including the possibility of future integrations as well as all required data layers. A centralized data hub should be established as early as possible, where all data is collected from different processes, different stages of the product life cycle, and over different facilities. Cloud-based platforms enable real-time data access and provide the required flexibility to the data flow. However, a risk-based approach should be taken to ensure data safety and integrity.

Non-integrated systems and a hybrid landscape of manual and digital data transfer require data bridges, which can be a combination of middleware solutions and manual data transfer. Due to the associated effort, manual data transfer should be optimized and focused on data that provides the most value to the process. Wherever possible, standardized protocols should be used to increase efficiency.

One of the biggest challenges lies in inconsistent data formats and variable data sources. A well-designed concept for data contextualization is required to enable aggregation of information over the complete process and to allow for powerful data analysis. Establishing a data hub with powerful information about the process provides a valuable resource, which is paramount for any sophisticated method for process characterization, like digital twins and the usage of artificial intelligence and machine learning methods.

VALIDATION CONSIDERATIONS FOR A FULLY AUTOMATED MANUFACTURING PLATFORM

Fully integrated platforms used in manufacturing of cell therapies combine multiple software and hardware components—such as

an MES, a LIMS, and analytics tools—into a unified ecosystem where data flows seamlessly without manual intervention. This integration must be validated to demonstrate that the platform consistently produces high-quality products.

Validation is defined as the documented process of demonstrating that a system, process, method, or piece of equipment consistently operates according to predetermined specifications and delivers results that meet quality standards. For the purpose of this article, the validation considerations will be focused on computer systems. Compliance with US Food and Drug Administration (FDA) regulations and guidance (e.g., 21 CFR Part 11) ensures that the systems function reliably and maintain data integrity throughout the manufacturing process.

For computer system validation (CSV) of automated cell therapy platforms, some considerations are listed in the next section related to system interoperability, data flow, testing, audit trails, security and access controls, and change management.

System Interoperability and Data Flow Mapping

System interoperability ensures seamless integration of components like the MES, the LIMS, and analytics tools. The MES must automatically retrieve batch records from the LIMS and send real-time data to analytics software for processing without manual intervention. For example, interface testing validates that communication between automated cell culture instruments and the MES is accurate and synchronized.

Understanding how data flows within the platform will ensure secure data transfers and data integrity. By creating a comprehensive data flow map for the platform, stakeholders can visually see where data originates, how it is processed, and where it ultimately resides within the platform. For example, cell viability data from automated microscopy must reliably transfer to the MES for tracking and analysis without corruption.

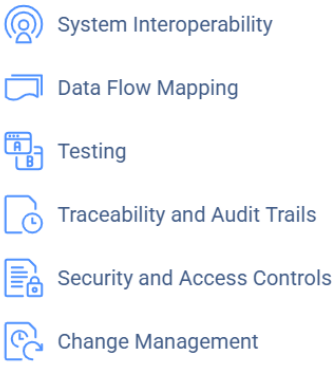
Testing

Testing the platform under real-world and peak operational conditions will ensure that the overall platform functions as intended. For example, stress testing the MES ensures it can handle a high volume of data when processing multiple patient batches simultaneously, maintaining system responsiveness and data accuracy during peak operations.

Traceability and Audit Trails

Robust audit trails ensure every action, event, and data modification is logged. For instance, any adjustment to temperature or gas levels in bioreactors must be recorded with a time stamp and user details in the MES. These tamper-proof records should be readily accessible for inspections or regulatory reviews. As many industry standard devices in ATMP come with limitations in supporting traceability, a holistic end-to-end process approach is essential. This includes a comprehensive audit trail, chain of identity, and chain of custody, integrating both digital solutions and manual interventions to ensure compliance with regulatory guidelines.

Figure 3: **Automated cell therapy platform validation considerations.**



Security and Access Controls

Security and access control validation protects sensitive data and limits unauthorized access. For instance, QC analysts should have permissions to modify analytical test data in the LIMS, whereas operators should be restricted to viewing data, ensuring secure role-based access.

Change Management

Change management ensures the validated state is maintained during system updates or modifications. For example, when upgrading MES software, testing must confirm compatibility with automation hardware and analytics tools before deployment, preventing disruptions in data communication.

CURRENT CHALLENGES AND LIMITATIONS

Despite rapid advances, several obstacles remain in implementing automation and data analytics.

1. Data integration: Merging datasets from multiple sources and instruments poses technical and logistical complexities.
2. Standardization: Divergent protocols and parameter definitions hinder cross-site and cross-platform process comparability.
3. Regulatory compliance: Automated systems must meet stringent data integrity and traceability requirements, necessitating significant investment in infrastructure.
4. Cost: High upfront expenses for automation equipment and software can be prohibitive, especially for smaller organizations.
5. Development time: The development time of ATMP processes is large due to limited starting material, process complexity, and incubation times.

The high cost of automation technology limits accessibility, and customizing processes for each patient increases complexity. Overcoming these hurdles requires collaboration among industry stakeholders, regulatory bodies, and academic institutions.

FUTURE DIRECTIONS AND INNOVATIONS

Anticipated developments in automation and data analytics are poised to further transform the cell therapy landscape. Blockchain for data integrity supports tamper-proof records, which will bolster traceability from cell harvest to patient infusion. This also enables seamless orchestration with healthcare providers for secure data sharing and coordinated patient care. Edge computing supports local data processing in manufacturing settings, which will enable faster decision-making and increase network resilience.

Advanced AI applications provide next-generation algorithms that could predict potential process deviations and proactively suggest corrective measures, streamlining production and enhancing quality. Emerging advancements in robotics, artificial intelligence, and machine learning are expected to make automated platforms more flexible and scalable. These innovations will address current challenges, improve process efficiency, and enable more cost-effective production, paving the way for broader access to CAR T cell therapies.

CONCLUSION

Implementing automated systems can streamline validation efforts by providing real-time monitoring, data-driven insights, and enhanced reproducibility. Automation also addresses key process validation challenges by standardizing workflows, minimizing operator variability, and enabling robust data collection for characterization. By integrating automation, manufacturers can improve process control and increase efficiencies to meet validation requirements.

In summary, the integration of automation and data analytics into cell therapy manufacturing offers immense opportunities for refining process understanding, consistency, and scalability. As data collection and analysis technologies continue to advance, industry stakeholders, regulatory agencies, and academic researchers alike must work together to address remaining challenges. Through collaborative efforts, cell therapies can be developed and produced more efficiently, ultimately increasing patient access to these potentially life-saving treatments.

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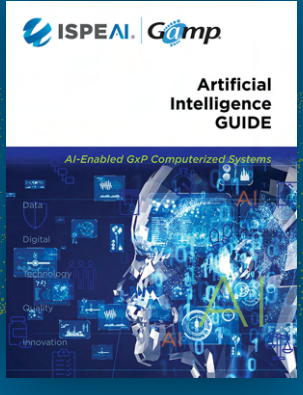

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FINAL PREPARATION of ATMPs at Point of Care

By Maria Rathmann Soerensen, PhD, Maria Amaya, PhD, Lesbeth C. Rodriguez, Sam Gunter, and Andrew Chang, PhD

Advanced therapy medicinal products (ATMPs), which include cell and gene therapy (C&GT) products, frequently require handling steps between quality control release and patient administration. These steps take place directly at the point of care and are especially critical for C&GTs with limited shelf life after preparation.

Regulators expect these activities to be performed within a Good Manufacturing Practices (GMP)-compliant environment, which introduces significant practical challenges for ATMP development and creates access barriers for patients. Why? Suitable GMP facilities are often unavailable near the point of care (POC).

REGULATORY FLEXIBILITY

This article calls for regulatory flexibility that permits the final preparation of ATMPs at the POC, or outside of GMP. This should be done using a framework of quality assurance measures that uphold patient safety and product consistency. Key quality measures would include:

- Only nonsubstantial manipulations, i.e., not considered GMP manufacturing steps, should take place at the POC for preparation of the ATMP.
- Generation of data should demonstrate robustness and consistency of the preparation process.
- Standardized, regulatory-approved instructions should be used at POC, adhering to good clinical practices (GCP).
- Training, accreditation, and oversight of personnel involved in the preparation process should be comprehensive.

GLOBAL HARMONIZATION

Global harmonization of quality standards for the final preparation of ATMPs prior to patient administration is vital for fostering faster, more widespread development and access to these therapies across regions. Consistent and transparent regulatory requirements for ATMP handling at the POC can help streamline the development pipeline and reduce barriers to patient access. Clear guidelines would mitigate the regulatory uncertainty surrounding POC preparation, which can otherwise delay product availability and limit market expansion. Harmonized standards would help accelerate ATMP accessibility globally, improve manufacturing predictability, and enhance patient safety by ensuring consistent quality and handling protocols across various healthcare settings.

BACKGROUND

ATMPs offer transformative potential for treating or even curing diseases that significantly impact patients' quality of life. These therapies include cell-based treatments—either autologous (derived from the patient) or allogeneic (from a donor)—as well as gene therapies, which may be administered in vivo (directly into the patient) or ex vivo (cells are genetically modified outside the body before administration). For ex vivo therapies, the path from cell collection (e.g., through apheresis) to patient treatment is intricate and often time sensitive, with the reconstituted cell product typically possessing a limited shelf life. Many of these therapies also require essential handling steps post-GMP release, such as thawing, washing, or buffer exchange, at the POC immediately before patient administration.

Potential regulatory expectations of strict GMP requirements on these final processing steps create significant operational hurdles for ATMP developers and can restrict patient access to life-saving therapies, as it is often challenging to locate GMP-compliant facilities near clinical sites. Therefore, it is essential to find a more adaptable regulatory approach that allows flexibility in GMP requirements for these POC processes. This flexibility would enable broader access to ATMPs, ensuring timely patient access to these advanced therapies while maintaining product quality and safety through tailored quality assurance measures.

A 2023 survey conducted by the Biotechnology Innovation Organization (BIO) highlighted that the majority of processing steps for ATMPs performed at the POC are carried out in either

open or hybrid systems by trained hospital personnel. These personnel follow established, regulatory-approved instructions that adhere to GCP. This ensures a consistent and standardized approach to handling. Survey respondents noted that for open systems, additional testing is commonly required to verify product quality and safety, reflecting the higher risk of contamination in an open environment. In contrast, testing requirements for closed systems were reported to be less frequent due to the reduced exposure to environmental factors, which inherently decreases the risk of contamination.

This distinction in testing requirements between open and closed systems underscores the need for a risk-based regulatory framework that accounts for system type and associated contamination risks. Such a framework would provide flexibility and support safe and efficient ATMP preparation at POC, ultimately facilitating broader patient access to these therapies while maintaining rigorous quality standards.

REGULATORY FRAMEWORKS

Current regulatory frameworks often lack clear guidance on the handling steps that are required after quality control (QC) but before the administration of ATMPs to patients, leaving sponsors uncertain about specific compliance requirements. Terminology for these critical processing steps varies widely across regions, with terms like "minimal manipulation," "preparation and modification steps," "processing steps," and "reconstitution activities" used interchangeably. This articles uses "processing steps." This inconsistency complicates regulatory compliance for sponsors by creating ambiguity around the necessary compliance pathways. The following is an outline of the major regulatory frameworks that currently serve as references for maintaining compliance in ATMP processing at the POC following batch release.

US Food and Drug Administration (FDA)

In January 2020, the US FDA released guidance titled "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)" [1], outlining requirements for gene therapy products that undergo additional handling after thawing. Additional release tests, including sterility and identity assessments, may be necessary to ensure the product's quality and safety if post-thaw manipulations, such as washing or culturing, are performed. This is especially true within an open system. The guidance also indicates that rapid sterility testing may be permitted for products with a short shelf life, particularly for ex vivo genetically modified cells that are either administered fresh or have a limited timeframe between final formulation and patient administration.

In recent discussions, the US FDA highlighted that certain activities carried out at the POC might be classified as manufacturing. These discussions include the FDA Center for Biologics Evaluation and Research(CBER) Office of Tissues and Advanced Therapies (OTAT) Town Hall on Cell Therapy Chemistry, Manufacturing, and Controls held 7 December 2022 [2]; the follow-up Town Hall on 8 June 2023 [3]; and the BIO/FDA Liaison meeting on 8 September 2023.

This classification applies particularly to procedures involving significant manipulation or those performed in open systems, which could trigger the need for additional on-site testing such as sterility, endotoxin, and identity assessments. To enhance compliance and protect product integrity during clinical investigations, the US FDA has advised sponsors to minimize handling steps at clinical sites following the manufacturing process. This approach is intended to streamline operations and ensure the highest quality standards are upheld throughout the therapy's life cycle.

In September 2020, the US FDA released an updated guidance titled "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" [4]. This revision supersedes the previous version issued in November 2017, which was later amended in December of the same year. The primary objective of the new guidance is to clarify the definition of minimal manipulation as outlined in CFR – Code of Federal Regulations Title 21, Section 1271.3 [5]. This clarification aims to assist stakeholders in effectively navigating the regulatory landscape surrounding human cells and tissues.

According to 21 CFR, Section 1271.3 [5], minimal manipulation is defined as follows:

- For structural tissue, any processing that does not change the original relevant characteristics of the tissue related to its function in reconstruction, repair, or replacement
- For cells or nonstructural tissues, any processing that does not alter the relevant biological characteristics of those cells or tissues.

The 2020 guidance [4] highlights that the original relevant characteristics of structural tissues are defined by the properties present in the donor that contribute to the tissue's functionality. Similarly, the biological characteristics of cells or nonstructural tissues include donor properties that influence their functions. Any alteration of these original characteristics raises safety and effectiveness concerns, making it difficult to predict how the product will perform after transplantation.

Consequently, determining whether human cells, tissues, and cellular- and tissue-based products (HCT/P) are minimally manipulated relies on the impact of manufacturing on these original characteristics in the donor, rather than on the intended use in the recipient. It is crucial to note that if there is insufficient information demonstrating that the processing aligns with the definition of minimal manipulation, the US FDA will classify the processing of a HCT/P as "more than minimal manipulation," thereby subjecting it to more stringent regulatory requirements.

A session entitled "Quality Standards for Final Preparation of Cell and Gene Therapy (C&GT) Products at POC" took place at the BIO International Convention in San Diego, California, in June 2024 [6]. During this session, the US FDA discussed their vision for the future of C&GT manufacturing, highlighting that much of the

production may take place at clinical sites. The following outlines the main highlights of the feedback received by the US FDA:

- The US FDA provided the example of using aseptically maintained closed systems for the manufacturing of CAR T cells directly at the clinic.
- For post-release manipulations at POC, the US FDA emphasized that risk assessment concepts remain relevant and should be applied based on the specific activities performed, the environment in which they occur, and the existing controls, including personnel training, accreditation, and oversight.
- For post-release testing following thawing, the US FDA indicated that sponsors must demonstrate effective control over their processes.
- The US FDA acknowledged that current standards need to be refined to better accommodate the unique challenges posed by advanced therapy products. For instance, waiting 14 days for sterility test results for products with a limited shelf life is impractical.

The US FDA also urged for greater collaboration between industry stakeholders and regulatory bodies to develop effective solutions that address these issues and enhance the overall framework for managing advanced therapies at the POC.

United States Pharmacopoeia (USP)

A similar approach is outlined in United States Pharmacopeia (USP) <1046> "Cell-Based Advanced Therapies and Tissue-Based Products," which underscores the essential elements of clinical site preparation and administration. The guidance states that "before the administration of certain cell or tissue-based products, one or more product modifications or preparative steps may be required" [7]. These modifications often occur close to the time of administration, potentially placing them outside the direct control of the original manufacturer.

USP <1046> [7] further elaborates on the nature of these product modifications or preparative steps, which may include:

- Change in final container: The manufactured product may need to be transferred from its original storage or transport container to a different one for administration.
- Change in physical state or temperature: Certain products may require thawing or warming to achieve the appropriate state for use.
- Change in solution or suspension: Some products may need to be dissolved, diluted, or suspended in a suitable liquid prior to administration.
- Combination with a biomaterial: Therapeutic cells might be combined with scaffold materials such as decellularized extracellular matrix sheets, gels, or other forms of biomaterials. Additionally, cells may be added to preexisting medical devices, like hollow-fiber filtration units, before use.
- Admixture or compounding: In some instances, mixing or compounding of cell products at the clinical site may be necessary.
- Filtration or washing: If the manufactured product contains unwanted materials, such as particulates or cellular debris, washing or filtration steps may be required to ensure purity.
- Sampling: Prior to administration, sampling of the final product may be needed to test the final formulation.

Furthermore, it is advised to monitor cell viability and potency post thawing for informational purposes, but release testing is not required at this stage before clinical deployment. Nevertheless, USP <1046> highlights that "cell-based therapy products that are prepared or modified at clinical sites need to be checked or tested appropriately to ensure they meet all quality specifications before being released for patient treatment" [7]. The extent and nature of these manipulations will determine whether additional release requirements or critical specifications are necessary beyond those established immediately after initial manufacturing. Thus, the need for further release testing of "clinical site–manipulated cell products" should be assessed based on the specific nature and extent of the manipulations performed.

European Commission and European Medicines Agency (EMA)

The EMA guidance titled "Guideline on Quality, Non-Clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products In Clinical Trials," [8] along with the European Commission's EudraLex document, "The Rules Governing Medicinal Products in the European Union, Volume 4: Good Manufacturing Practice, Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products" [9], delineates essential considerations regarding processing steps in the context of ATMPs.

These guidelines specify that processing steps involve actions taken after batch release and before administration to patients, which may take place outside of a GMP environment. A key point made in these guidelines is that any procedure involving substantial manipulation cannot be classified as processing steps. Each step in processing must be accompanied by a justification for why those activities were not completed during the manufacturing phase prior to batch release.

The European Commission's EudraLex document [9] lists the following examples of processing steps:

- Thawing and washing: This involves thawing the product, washing it, and performing buffer exchange, including centrifugation to eliminate preservation solutions—such as dimethyl sulfoxide (DMSO)—and to remove process-related impurities, such as residual preservation solution and dead cells, potentially through filtering.
- Resuspension and dilution: This step entails resuspending, dissolving, or diluting the product with an appropriate solvent or buffer to prepare it for administration.
- Mixing: The product may need to be mixed with the patient's own cells, an adjuvant, or other substances required for administration, including matrices. However, it is crucial to note that mixing a gene therapy vector with autologous cells is classified as a manufacturing activity and must be conducted under GMP.

- Splitting doses: This includes dividing the product for separate doses and adjusting dosages based on specific requirements, such as cell count.
- Loading for delivery: This encompasses loading the final product into delivery systems or surgical devices and transferring it to an infusion bag or syringe for administration.

For authorized ATMPs, it is essential that the processing steps are validated to ensure that these steps do not adversely affect the quality, safety, or efficacy profile of the ATMP. Notably, such processing step activities are not deemed substantial manipulation, and the associated risks are generally considered lower compared to GMP manufacturing processes involving more complex substantial manipulation [9].

Pharmaceutical Inspection Co-Operation Scheme (PIC/S)

According to the PIC/S "Guide to Good Manufacturing Practices for Medicinal Products. Annex 13" [10], processing steps of investigational medicinal products (IMPs) is defined as a process that is generally not regarded as manufacturing, unless specific national laws state otherwise. As such, this guideline does not encompass processing steps activities. The term "reconstitution" refers specifically to the straightforward process of dissolving or dispersing an IMP for administration to a trial subject. This may also include diluting or mixing the investigational product with other substances that act as a vehicle for its delivery.

It is essential to clarify that reconstitution or processing steps do not involve the mixing of various ingredients—including the active substance—to create the IMP itself. Instead, for a process to be classified as processing step, the investigational medicinal product must already exist prior to the procedure. Additionally, the processing steps should ideally take place as close to the time of administration as possible to ensure product integrity and efficacy. This procedure must be thoroughly outlined in the clinical trial application dossier and made readily accessible at the clinical trial site, ensuring that all personnel involved are aware of and adhere to the defined protocol.

This distinction between processing steps and manufacturing is critical for compliance with regulatory expectations and maintaining the quality and safety of investigational therapies. By clearly defining the parameters of processing steps, the PIC/S guidelines aim to provide a framework that supports the safe and effective administration of IMPs while minimizing the risks associated with handling complex therapeutic products. Proper documentation and adherence to established protocols can help ensure that processing steps do not compromise the integrity of the investigational medicinal product, ultimately contributing to the success of clinical trials.

World Health Organization (WHO)

In May 2023, the WHO released a technical document titled "Considerations in Developing a Regulatory Framework for Human Cells and Tissues and for Advanced Therapy Medicinal Products, Annex 3" [11]. This document aims to support regulatory convergence and reliance for human cell therapies and ATMPs worldwide, promoting consistent regulatory practices across jurisdictions. By fostering a globally harmonized regulatory framework, the WHO seeks to facilitate the development, safety, and accessibility of these advanced therapies. The guidance provides a comprehensive foundation for the effective oversight of HCTs and ATMPs, including definitions, product categorization, and a risk-based approach to regulation, each designed to ensure quality, safety, and efficacy.

The WHO document specifies that minimal manipulation involves processing cells or tissues in ways that do not significantly modify their original structural integrity, functional properties, or safety profile. This definition is intended to differentiate between simple, low-risk processing and substantial manipulation, which requires greater regulatory scrutiny. Minimally manipulated cells and tissues are expected to perform their primary function locally without a systemic effect and must rely solely on their inherent metabolic activity.

Recognized minimal manipulation procedures include sizing, rinsing, and saline washing. Additionally, certain regional regulatory frameworks may permit more extensive procedures under the minimal manipulation classification, such as cutting, grinding, centrifugation, freeze-drying, antibiotic treatment, sterilization, and cryopreservation, depending on the risks associated with these processes and their impact on the tissue's structural and functional characteristics.

In the context of POC applications, minimal manipulation is crucial for defining permissible on-site processing steps that healthcare providers can perform immediately before administration without needing a full GMP environment. By limiting POC activities to minimal manipulation, the WHO guidance could be applied to reduce the complexity and cost associated with manufacturing ATMPs while ensuring that the quality, safety, and efficacy of the product remain intact for the patient's benefits.

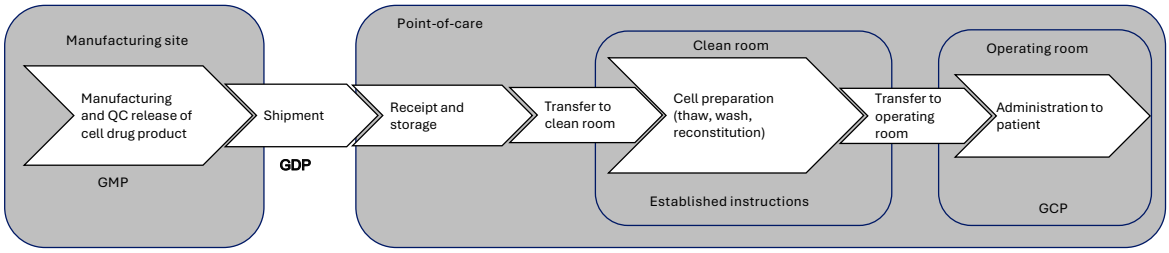
RISK MITIGATION APPROACHES

A comprehensive risk assessment that encompasses all processing steps, post-release testing, and pre-administration activities is essential. This helps ensure that these procedures do not adversely impact the quality, safety, or efficacy of C&GT products when conducted at the POC. Each preparation step should undergo an evaluation to identify potential risks and relevant mitigations needed to maintain product integrity and patient safety. The importance of this risk assessment is underscored in various regulatory guidelines, including PIC/S Annex 13 [10], ICH Q9(R1) [12], and associated GMP standards. In addition to the risk assessment, site qualification is a critical factor for the success and regulatory compliance of POC administration. Key components of site qualification include the following.

Personnel Training

It's necessary to ensure that all personnel involved in product

Figure 1: Here we demonstrate an example of the pathway an allogeneic cryopreserved cell product takes from a GMP-certified manufacturing facility to the point-of-care (POC)POC, detailing the essential steps required to prepare the final product for patient administration. In this scenario, the POC is a tissue establishment authorized by local health authorities for tissue transplantation. At the POC, cell handling procedures, considered processing steps activities under EMA guidelines, are performed following specific, established protocols. These protocols are reinforced by thorough personnel training and supported by a robust quality management system in place at the POC. This approach has been approved for a clinical phase 1 study in both Europe and the UK.



handling and administration are adequately trained in both site-specific and sponsor-specific standard operating procedures (SOPs). This training should cover all relevant protocols for preparation, storage, handling, and administration of the product, with a focus on maintaining quality and compliance with relevant SOPs.

Qualification of Process Steps

Qualification of steps performed at the POC is critical in ensuring the safety, efficacy, and consistency of ATMPs. Because POC environments are less controlled than centralized manufacturing facilities, validating each step of the preparation process helps confirm that products meet the required quality standards. Furthermore, procedures implemented at the POC site should include detailed instructions for the storage and handling of the product to prevent degradation or contamination. This should include protocols to maintain complete traceability, especially for autologous products.

For autologous cell therapies, traceability is particularly crucial to ensure that products are accurately matched to each individual patient. It prevents cross-contamination or misidentification. This comprehensive approach to risk assessment, site qualification, and procedural compliance helps safeguard the therapeutic efficacy and patient safety of ATMPs administered at the POC.

CASE STUDY: ALLOGENEIC CRYOPRESERVED CELL THERAPY MEDICINAL PRODUCT

Figure 1 provides an example of the pathway an allogeneic cryopreserved cell product takes from a GMP-certified manufacturing facility to the POC, detailing the essential steps required to prepare the final product for patient administration. In this scenario, the POC is a tissue establishment authorized by local health authorities for tissue transplantation. At the POC, cell handling procedures, considered processing steps activities under EMA guidelines, are performed following specific, established protocols. These protocols are reinforced by thorough personnel training and supported by a robust quality management system in place at the POC. This approach has been approved for a clinical phase 1 study in both Europe and the UK.

Rationale for Processing Steps at POC

The rationale for conducting processing steps at the POC relies on maintaining the high quality and stability of the cell-based drug product during transport and storage, and ensuring it is safe for patient administration. Cryopreservation is essential to protect cells through transit to the POC and during storage prior to use. However, after thawing at the POC, the drug product cannot be administered directly from the vial because the cryopreservation medium contains DMSO and other cell culture reagents, which are not suitable for direct injection into patients. If these components are not removed and replaced with an excipient-grade buffer appropriate for human administration, they could lead to local toxicity at the injection site, posing significant safety risks to the patient.

Thus, washing and reconstituting the cells at the POC is a critical step. This process removes the cryopreservation medium, minimizing potential adverse reactions and ensuring the drug product meets necessary safety standards. Processing steps at the POC also helps maintain cell viability and therapeutic functionality, as the cells can be quickly prepared in a controlled environment and administered shortly thereafter, reducing the time between thawing and patient use. By performing these steps at the POC, healthcare providers can more effectively manage risks associated with cell handling and enhance the overall safety and quality of the final product administered to patients.

Cell Handling Strategy

The processing steps for the drug product at the POC involve a streamlined process of thawing, washing, and resuspension, specifically designed to minimize handling and reduce the potential for error. The washing step is implemented immediately

Table 1: Examples of mitigation and control of risks to safety and quality of cell products related to the handling of an allogeneic cell product at POC.

Step	Risk	Mitigations and Control	Responsibility
Receipt	**Traceability**	Unique numbering of each drug product vial	POC
		Information technology (IT) system (RSTM) to manage medication dispensing per study participant	POC
		Established procedures for bidirectional tracing back to donor	POC
		Label control according to trial medication manual	POC
		Use of established cell handling instructions, including documentation of each step in formulars and QC review of these before patient administration	Sponsor/POC
Storage	**Stability** (i.e., the preestablished drug product stability may be compromised)	The drug product vials are transported using a designated and validated precooled transporter to the nitrogen tank for storage until use	POC
		Visual inspection that the vials are still frozen when removed from transporter	POC
Thaw	**Potency/strength** (i.e., the cell concentration and viability may be incorrect)	Thawing performed in an automated thawing instrument	POC
		Cell concentration and viability assessed prior to patient administration	POC
Washing and resuspension	Microbial safety (i.e., the drug product may be contaminated during aseptic cell handling)	Qualification/training of personnel in the aseptic cell preparation process	Sponsor/POC
		Establishment and use of cell handling instructions, including documentation of each step in formulars and QC review of these before patient administration	Sponsor/POC
		Handling of the cells in a controlled environment	POC
		Rapid microbial test and compendial sterility test of the spend washing solution	Sponsor/POC
		Follow-up procedure in case of positive microbiological test result	Sponsor/POC
		Prophylactic antibiotic treatment and careful clinical monitoring of the study participants	Sponsor/POC
Potency/ strength	Reduced cell count, viability, homogeneity in suspension, and stability	Qualification of personnel	Sponsor/POC
		Establishment and use of cell handling instructions, including documentation of each step in formulars and QC review of these before patient administration	Sponsor/POC
		Equipment in control	POC
		Verification of cell count and viability post cell handling	POC
		In-use stability studies covering cell preparation procedure	Sponsor
		Resuspension of cell suspension just prior to loading the device	POC
		A final QC review of cell preparation documentation before administration	POC

after thawing to effectively remove the cryopreservation medium, thereby preserving cell integrity and quality. Following washing, the resuspension step adjusts the cells to the intended concentration, ensuring accurate dosing for patient administration. This handling procedure is classified as simple aseptic processing and is performed under the quality system already established at the POC tissue facility. The controlled environment, combined with trained personnel and procedural oversight, ensures that these processing steps are carried out with high precision and safety.

Risk Evaluation

A thorough risk assessment was conducted using the failure mode and effects analysis (FMEA) method, which involved evaluating and assigning ratings for the severity and probability of occurrence of each identified risk, following the guidelines set forth in ICH Q9 R1 and ISO 14971 [12, 13]. This assessment highlighted several key risks, including:

- Microbial safety: The potential for microbial contamination during the aseptic handling of cells poses significant risks to the safety of the product.

- Potency and strength: Risks associated with inaccurate cell counting, diminished cell concentration or viability, inconsistency in cell suspension homogeneity, and reduced stability of the drug product can severely impact its effectiveness.
- Traceability: Ensuring the traceability of vials from the moment they arrive at the POC until administration to the study participant is crucial for maintaining oversight and accountability.

To effectively address these risks, various mitigation strategies were put in place, focusing on ensuring thorough personnel and site qualification. This involved the development of specific process instructions and documentation templates, with confirmatory QC testing of the cell product prior to its use. Table 1 provides a detailed overview of the risks associated with each stage of the process, the corresponding mitigation strategies, and the designated roles responsible for implementing these actions.

Site Qualification

The POC site serves as a licensed tissue establishment authorized by local health authorities to manage and perform tissue and cell transplants. A thorough qualification process was undertaken to ensure that the site meets stringent quality standards. This involved an auditing procedure by the sponsor, which confirmed that the POC had implemented a robust quality management system. The findings indicated that the facility is equipped with a controlled environment tailored for aseptic cell handling, supported by the necessary SOPs designed to maintain both the facility and its equipment in a state of continuous control. This thorough assessment validated the POC's capability to perform its intended functions safely and effectively.

Cell preparation at the POC is conducted within a cleanroom that adheres to aseptic techniques to mitigate contamination risks. The actual handling of the cell product is executed on a monitored laminar flow (LAF) bench, which provides a sterile environment essential for maintaining cell integrity. To ensure compliance with environmental safety standards, environmental monitoring is regularly performed using settle plates during process qualification runs.

These assessments have confirmed the effectiveness of the LAF bench in providing a sterile environment. They support the overall safety and quality of the cell preparation process prior to patient administration. This meticulous approach underscores the commitment to maintaining high standards in the handling and processing of cells at the POC.

Qualification of Cell Handling and Staff Training

Several qualification runs were performed by two separate operators, and the sterility of the handled cell product was validated using the European Pharmacopoeia (Ph. Eur.) compendial sterility method. To further ensure the integrity of the aseptic handling procedures, the team conducted aseptic process simulations, commonly referred to as media fills. Personnel tasked with cell preparation underwent extensive training focused on aseptic techniques, washing, and resuspension processes. They were also trained on the specific cell preparation protocols and had to demonstrate their proficiency in producing a sterile cell product that met the required concentration and viability standards.

> As ATMPs continue to advance in medical innovation, the capability of community hospitals to administer these treatments becomes crucial.

Assuring Traceability

At the POC, a comprehensive bi-directional traceability system was established to track each patient's treatment back to the original donor. Each vial is equipped with a unique identification number, and an integrated IT system was implemented to oversee the dispensing of medication for all participants. This system offers the sponsor detailed visibility throughout the entire life cycle of the vials, encompassing storage, transit to the POC, receipt, dispensing for clinical administration, and thorough drug accountability and vial reconciliation. Additionally, label control processes adhere strictly to the guidelines outlined in the trial medication manual and the cell handling instructions, with every manual entry subject to verification by a second individual to guarantee precision and regulatory compliance.

Processing Steps at the POC

The following instructions specific to the cell handling procedure were included in the clinical trial application to ensure a standardized approach during the preparation of the drug product for study participants.

Preparation of resuspended cell product for administration

This instruction aims to guide personnel responsible for the thawing, washing, and resuspension of the drug product prior to transplantation. It outlines the necessary steps to ensure successful preparation and requires documentation of adherence to the procedure. The instructions are printed and utilized as a participant-specific preparation record during the handling of the trial product. Upon completion, the document and its attachments must be filed in the investigator trial master file. In cases where deviations occur during cell preparation, the individual in charge of cell handling must consult with the designated approver before proceeding further.

Instructions for handling resuspended cell product in the operating room

This section details the necessary steps for loading the cell suspension into the injection device within the operating room. The medical doctor responsible for the transplantation procedure oversees this process. Additionally, the cell handling personnel designated at the study site must possess prior experience with cell handling and have undergone training specific to the procedures outlined in the study protocol. This ensures that all actions taken during the cell handling process are executed with the utmost care and expertise.

Testing of the Final Product

To ensure cell quality with regard to sterility, both a rapid microbial test and a compendial sterility test were performed on spent media collected during the cell washing step. The rapid microbial test provided an immediate indication of any microbial contamination, preventing the administration of an unsterile product. Given that the compendial sterility test results would only be available after administration, any positive sterility test result would be logged as a serious adverse event.

In such cases, the participant would immediately begin appropriate antimicrobial treatment, and the treatment of new patients would be paused until the contamination source was identified and corrective actions were implemented. Verification of cell concentration and viability was conducted on the final cell suspension after all cell handling steps but before patient administration. If either cell concentration or viability fell outside the acceptable range, the cell suspension would be discarded to maintain product safety and efficacy.

CHALLENGES FOR PROCESSING STEPS AT THE POC

Implementing GMP standards for processing steps at the POC involves a careful balance of patient safety and accessibility challenges. Although GMP compliance aims to reinforce patient safety and product quality, it may inadvertently limit patient access to advanced therapies. First, only a limited number of hospitals are equipped to meet stringent GMP standards, reducing the availability of cell therapies to fewer facilities. This limitation is especially impactful in rural or underserved areas, where access to GMP-compliant facilities is scarce. Additionally, patients may face longer travel distances to reach GMP-certified centers, creating obstacles for those with mobility constraints or limited financial resources.

Adding to this complexity, regulatory expectations for C&GT processing vary widely across global jurisdictions, driven by differences in healthcare systems, regulatory frameworks, and risk management priorities. For instance, the EMA allows some POC processing activities to be performed outside of GMP, a decision that supports faster access to these critical therapies. This approach contrasts with other regions where GMP requirements are more stringently enforced, regardless of the product's location or processing steps needs.

The different characteristics of each cell therapy product and related POC handling strategy pose a challenge to harmonization of POC regulatory expectations. Nevertheless, such harmonization is indeed needed to minimize the current variations across POC sites due to different practices and expectations in different regions, and it would help assure that the reconstitution activities do not impact safety and efficacy of the product administered to patients across countries.

QUALITY AND SAFETY

According to a 2023 survey conducted among BIO members, processing steps at the POC site are primarily performed outside traditional GMP facilities, often in open or hybrid systems. To uphold the quality and safety of the final product prior to patient administration, it is essential to establish robust procedural, handling, and environmental controls. Key strategies to achieve these controls involve:

- Applying GMP and GCP principles
- Using closed systems wherever possible
- Maintaining aseptic conditions during open processing steps
- Following strict written procedures with thorough documentation

Staff Training

Staff training is also fundamental to maintaining these standards and ensuring procedural compliance. Currently, the administration of commercially available ATMPs is limited to a select number of tier 1 FACT-accredited transplant centers and academic medical centers within the US, along with similar high-standard facilities worldwide.

This limitation poses significant access barriers, as only a fraction of patients have access to these specialized centers equipped for ATMP delivery. To address product quality assurance at POC, the US FDA has indicated that additional release testing, including sterility and identity assessments, may be necessary to validate these therapies prior to administration. This further underscores the critical need for stringent quality measures outside of traditional GMP environments.

STERILITY TESTING EXEMPTIONS

Under 21 CFR 610.12 and 21 CFR 1271.155 [14, 15], cell therapy products may be exempt from sterility testing if processed in closed systems without manual handling, pending a case-by-case risk assessment. However, most POC processing, especially during early clinical phases, involves open or hybrid systems, which makes meeting these exemption criteria challenging. To navigate this, detailed guidance documents are needed to support consistent application of sterility standards. Such documents should outline specific controls and testing strategies tailored for open and hybrid processing systems, helping POC facilities maintain product quality and expand access to cell therapy treatments while adhering to essential regulatory standards.

When determining sterility testing requirements, a comprehensive approach is critical. This involves integrating microbial

contamination risk mitigation strategies, such as robust process controls, continuous active monitoring of aseptic practices, environmental monitoring, and the use of suitable facilities. Additionally, a rigorous training program for personnel engaged in aseptic processing is crucial, especially given that sterility testing results often become available only after patient administration. Establishing these layers of control ensures that even without immediate sterility results, the final product meets safety standards, reducing patient risk associated with microbial contamination.

THE NEED FOR TRACEABILITY

The case study in this article highlights the critical role of a robust bi-directional tracing system that tracks cell therapy products from the patient back to the donor, ensuring identity and safety without the need for additional identity testing. At the POC, each vial is uniquely labeled for each patient, allowing for comprehensive traceability throughout the product's life cycle—from drug product release through administration.

This patient-specific labeling and tracking system grants the sponsor and clinical teams full oversight of each vial's journey, meeting regulatory standards and enhancing patient safety. By using automated or semi-automated systems integrated with patient records, this approach minimizes potential errors and enables swift reconciliation. Such systematic control and verification steps effectively eliminate the need for extra identity testing, as each phase of handling is safeguarded by rigorous tracking protocols.

NEW POC SITES

Adding new POC sites during clinical development and after marketing authorization application/biologics license application (MAA/BLA) approval is an area where regulatory flexibility is essential to support patient access without compromising product safety and quality. Introducing ATMP preparation and administration at a new POC site requires a comprehensive risk assessment to evaluate any potential variability introduced by the new setting, particularly concerning the complexity of the processing steps involved.

This risk assessment should be complemented by established procedural controls, such as standardized instructions, a robust personnel training program, and rigorous facility qualification processes. Ensuring alignment with GCP principles can help maintain high standards, ideally allowing new POC sites to operate without necessitating separate regulatory approvals. This approach supports both quality and accessibility, enabling wider patient access to ATMPs across various clinical settings.

IMPROVEMENTS

As cell therapy products progress through mid-to-late stages of clinical development, advancements in the processing steps often emerge. Examples of this include the development of fully closed systems or optimized cryopreservation methods. Although these improvements necessitate comparability studies [16, 17] and requalification of the processing steps, they also highlight the importance of regulatory flexibility to enable seamless transitions; for instance, moving from open handling in a controlled aseptic setting to closed handling in a more adaptable environment.

Building a robust network of qualified treatment centers is essential not only for delivering consistent and high-quality care, but also for advancing the development of personalized ATMPs.

A phase-appropriate, risk-based regulatory framework that encourages developers to refine and simplify the processing steps, while prioritizing product quality and patient safety, would support these advancements. Such a framework should strike a balance between rigorous standards and practical implementation, helping both patients and developers navigate this evolving field. Ultimately, a harmonized global approach to regulatory requirements for processing steps at the POC is essential to make these advanced therapies widely accessible.

CONCLUSION

The uncertainties of regulatory requirements for the final processing steps of ATMPs remain a considerable barrier to making these therapies globally accessible. Establishing a regulatory framework that does not define the POC reconstitution activities as GMP production steps and allows the developers to adhere to high-quality standards—such as the established accreditation and oversight at POC sites and adherence to GCP—could greatly enhance patient access without compromising safety or product quality. This approach is particularly important for patients who face logistical or financial limitations making difficult to travel to treatment centers, thus helping democratize access to advanced therapies.

As ATMPs continue to advance in medical innovation, the capability of community hospitals to administer these treatments becomes crucial. Building a robust network of qualified treatment centers is essential not only for delivering consistent and high-quality care, but also for advancing the development of personalized ATMPs. Embracing flexibility in product preparation requirements, paired with stringent quality assurance, will support a sustainable pathway for scaling ATMP treatments, benefiting a broader patient base.

Aligning with established guidelines and adopting a phased, risk-based regulatory approach will be key in shaping a supportive

regulatory landscape for C&GT. Through collaboration among stakeholders, this balanced approach will drive broader patient access, accelerate therapeutic innovation, and propel the field forward, ensuring more individuals can experience the transformative potential of these therapies.

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UNLOCKING ATMPs:
Reducing Cost as an Obstacle to Patient Access

By Tabea Martins

Advanced therapy medicinal products (ATMPs) have the potential to treat life-threatening, incurable conditions. But access to these therapies remains challenging due to the nature of current ATMP manufacturing models. This article explores solutions, focusing on standardized processing and shared knowledge as gateways to automated, robotic manufacturing and decentralized production.

BACKGROUND

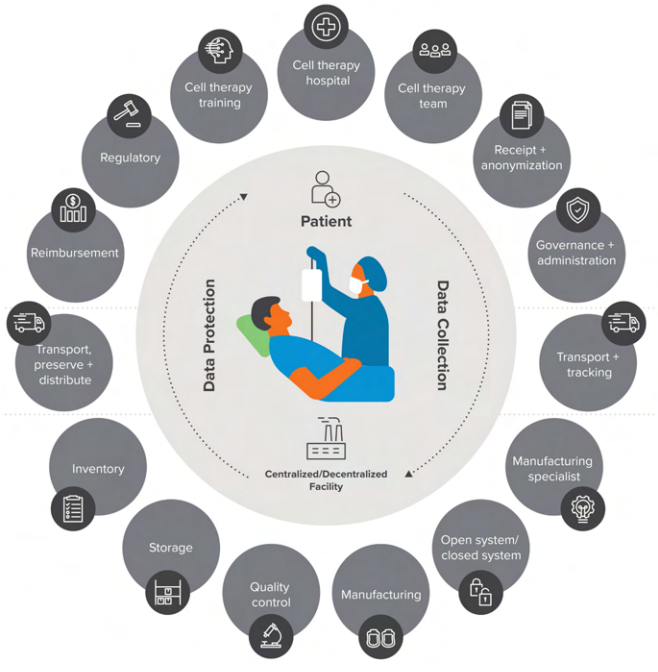
Using engineered cells, genes, and tissues, ATMPs have the potential to precisely target the root cause of cancers, rare diseases, and other previously incurable conditions. They are distinct from traditional biologics in several ways [1], notably by their reliance on living source material derived from a donor, or, in the case of personalized therapies, from a patient's own cells.

Life science manufacturers worldwide are drawn to the curative potential of these therapies. A 2023 survey of more than 500 manufacturers showed that 83% have cell therapies in their pipeline [2]. Gene therapy programs are attracting significant investment and research, with several advancing from preclinical research to commercial launch [3].

To unlock the full promise of these innovative therapies, manufacturers, payers, and government agencies must address the issue of patient access, particularly from the perspective of cost control. Policy reform and innovative payment models are part of the solution [4]. Regulations designed to streamline the clinical trial process would help lower cost, for example. Concepts such as innovative contracting—in which payers and manufacturers agree to outcomes-based reimbursement or other models meant to address uncertainty—could also improve patient access [5].

Further upstream, collaborations between drug manufacturers, equipment vendors, regulators, hospitals, and academic and public institutions are driving new approaches to ATMP manufacturing—approaches that open the door to standardized processes, simpler facilities, and less costly manufacturing models. Decentralized systems, for example, could put ATMP production units close to a patient's bedside, facilitating a strong knowledge-sharing network and eliminating the complex supply chains that impede rapid, cost-effective delivery. Decentralization is already in practice in some markets and could transform the future of manufacturing for certain ATMP modalities [6]. To

Figure 1: The cell therapy manufacturing chain.



reach that future, ATMP manufacturers must document today's challenges. From that foundational understanding, collaborators across the industry can lay the groundwork for emerging solutions and practices that will bring much-needed therapies to patients.

MEETING CURRENT MANUFACTURING CHALLENGES

The term "vein-to-vein" often appears in the context of personalized medicine, referring to the manufacturing life cycle that typically begins with the collection of patient or donor cells and ends with the bedside administration of a final therapy. Between those "veins" lies a lengthy process (see Figure 1). Simplifying that process is the key to improved patient access. To do that, one thing is necessary above all: an ecosystem of shared knowledge.

IMPROVED ACCESS THROUGH SHARED KNOWLEDGE

In the traditional biologics industry, confidentiality is often prioritized over collaboration. Large, well-established companies rely on proprietary intellectual property to compete for global market share. The ATMP industry is different: to move forward against the headwinds of significant manufacturing and distribution challenges, stakeholders in this industry need open dialogue, adaptive co-learning, and consistent knowledge transfer strategies [7].

Cross-functional, ATMP-focused partnerships are emerging around the world in response to that need. The European Union (EU)-funded JOIN4ATMP is a recent example. Launched in early 2024, it "brings together all members of the European University Hospital Alliance with the existing EU-funded T2EVOLVE and RESTORE networks, and with active support from industry partners and patient representatives as core partners" with the goal of ensuring "a holistic assessment of current hurdles and the best way to improve support and regulation of ATMP development and use" [8, 9].

Consortiums like this are the key to addressing the long timelines, significant complexities, and high costs associated with the ATMP manufacturing chain [10]. By working together to understand these challenges, stakeholders across this industry can multiply their positive impact across diverse fronts. The JOIN4ATMP consortium, for example, aims to drive outcomes from the perspective of scientific advancement, quality of life for patients, social and structural improvements, and economic and technological gains [11].

SCALABILITY CHALLENGES

For manufacturers of personalized therapies, each batch is patient-specific, precluding the possibility of bulk scaleup. Multistakeholder organizations, like the Alliance for Regenerative Medicine, seek to help ATMP manufacturers address scalability issues. This is done by understanding current manufacturing constraints and codeveloping solutions in response [12, 13].

COMPLEXITY OF THE MANUFACTURING PROCESS

With ATMPs still relatively new compared to other life science modalities, many companies in this submarket have not yet fully characterized and standardized their manufacturing processes, leaving them reliant on manual interventions. This has added to the challenge of transitioning from research and development (R&D) to a commercially viable, GMP-ready manufacturing platform [14].

In response to these manufacturing challenges, many of today's ATMP research teams are working in partnership with equipment vendors and point-of-care institutions looking for solutions. Robotically driven ATMP manufacturing platforms are one promising result of these partnerships, making it possible for manufacturers to automate their processes and thereby improve their reliability and scalability [15].

REGULATORY HURDLES

The streamlined approval pathways designed to accelerate compliance for traditional drug manufacturers don't always apply in the context of these novel therapies. Regulatory requirements may vary from region to region, for example, and different agencies may update their regulations at different times, creating a lag between ATMP innovations and related regulations [16]. Challenges like these can make it difficult for manufacturers to navigate the regulatory environment. For example, the "EU GMP Annex 1: Manufacture of Sterile Medicinal Products" guideline, which was recently updated, may apply to ATMPs, which require aseptic handling. However, the European Commission's stand-alone ATMP guidance states that no other annexes are applicable [17].

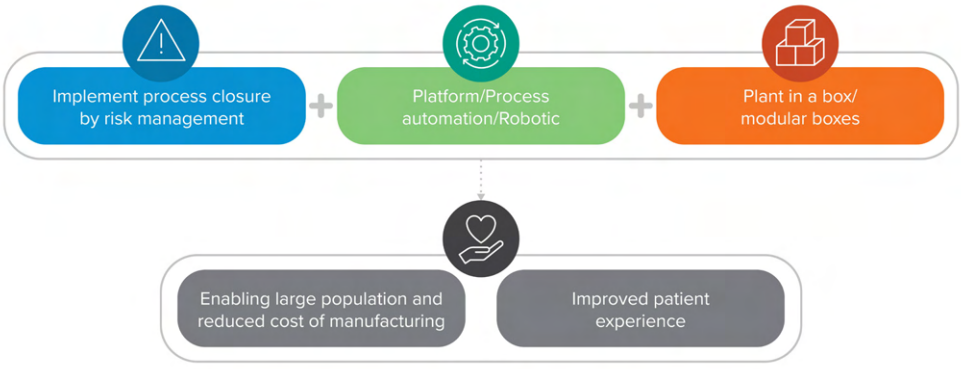
Regulators and manufacturers must face these compliance challenges together. By engaging with each other early, these stakeholder groups can codevelop and validate a strong risk-based approach to commercial-scale ATMP production. This approach can help prioritize consistency, quality, and, above all, patient safety [16].

SUPPLY CHAIN COMPLEXITY

Once collected from a patient or donor via apheresis or biopsy, the cellular material that begins a cell therapy manufacturing process is typically cryopreserved and transported to the manufacturing site for processing (or transported "fresh" if it can reach the manufacturing facility rapidly). Once the production process is complete, the sensitive live-cell therapies follow the same journey in reverse, moving from the manufacturing site to the patient's bedside for administration.

Extensive cold chain logistics are required to preserve the quality of these "living" materials while they're in transit or storage, including robust temperature and storage controls. Manufacturers must also establish a sophisticated end-to-end tracking system to maintain chain of identity and chain of custody, especially when handling personalized therapies where the consequences of a misidentification or mix-up are severe. By working closely with logistics partners and healthcare institutions, manufacturers can codevelop logistics and supply innovations that aim to simplify these dynamics and accelerate the manufacturing life cycle.

Figure 2: A pathway to reduced manufacturing costs and improved access.



THE FUTURE OF ATMP MANUFACTURING

If these challenges seem insurmountable, take heart from reflecting on the biotech boom of the 1980s, when the first monoclonal antibodies (mAbs) emerged on the market. At the time, the process of making these pioneering therapies was lengthy, manual, and highly customized, which elevated their market price [18]. After four decades of innovation and improvement, the mAb manufacturing process is well-understood and highly standardized.

Current ATMP pioneers are at the beginning of a similar evolutionary curve. As illustrated in Figure 2, this evolution will depend on technological advances that enable future scalability and speed through closed, automated, and modular processing. Cross-industry collaboration and shared knowledge are the keys to making this future a reality.

To understand how today's ATMP manufacturers might prepare for this future, the following sections will examine a few of the many vital trends and advancements currently shaping this submarket, particularly in the area of personalized cell therapies.

Process Standardization

Here we discuss process standardization for a robotics-ready, automation-optimized cell therapy process. Shifting from customized, operator-driven processes to a standardized process platform is critical to the future of commercial-scale ATMP manufacturing.

Standardization lays the groundwork for a GMP-ready process that yields safe, pure, and reproducible therapies of the highest possible quality [16]. Without a standardized process, manual interventions in open processing environments are required. This type of operator-driven approach can drive up the size and cost of production spaces, slow the manufacturing process, and expose in-process substances to the risk of contamination. Standardization addresses these issues by opening the door to automation and robotic or cobotic processing, which is the key to manufacturing safe, pure, and reproducible cell therapies in a scalable GMP environment.

Getting there requires cell therapy innovators to scrutinize their decisions during R&D, looking for ways to eliminate manual actions and develop repeatable protocols that prioritize simplicity, process control, and commercial-scale efficiency.

Closed Process-In-A-Box Systems

Robotics-driven process-in-a-box platforms used within closed processing offer a more scalable and flexible cell therapy manufacturing model. Standardization is the gateway to a manufacturing model that's transforming the landscape of ATMP manufacturing: process closure.

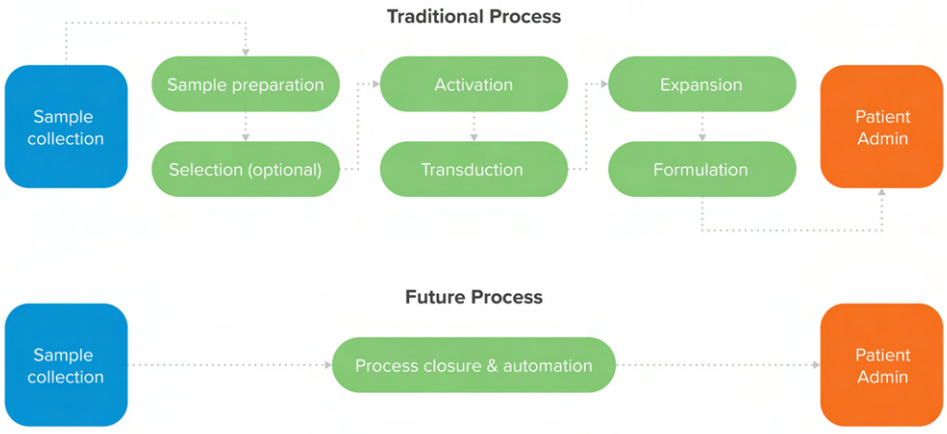
Historically, manufacturers have mitigated contamination risks by locating open process steps in highly controlled cleanroom environments. But cleanrooms are imperfect—they require energy-intensive heating, ventilation, and air conditioning systems; strict operational protocols; and a level of customization that can make them challenging to repurpose as demand shifts.

Closed processing offers an alternative. By leveraging modular process-in-a-box systems, manufacturers can shift the burden of segregation from room-level environmental controls down to the equipment itself. The benefits of such a shift are numerous, particularly for cell therapy manufacturers intent on solving persistent scalability challenges. Closed process-in-a-box systems enable new, more flexible manufacturing models, such as decentralized manufacturing (examined next) and multimodal processing.

By reducing or eliminating the need for strictly controlled environments, process-in-a-box systems also enable simpler and more flexible facilities that cost less to build, run, and maintain. Most importantly, process closure is key to product quality. Through a scientifically driven risk-managed approach, manufacturers can identify the unique risks embedded in their process—risks that may be addressable in part through robust process closure. Because closed systems move process steps into a highly repeatable and automation-driven system of advanced robotic or cobotic technologies, there's a lower risk of batch-to-batch variability or other quality issues [19].

How close is the future of fully automated, robotics-driven process closure for ATMP manufacturers? Several established systems exist today and are often used in the cell therapy context,

Figure 3: Standardization enables closed processing.



including Milteny Biotec's CliniMACS Prodigy [20], Lonza's Cocoon Platform [21], and Cytiva's Sefia Select system [22]. Other promising systems are currently in development, such as the Constellation by Cellular Origins [22] and a collaboratively developed robotic manufacturing platform by Cellular Origins and Cytiva [23].

However, many manufacturers are relying for now on a hybrid approach, in which they leverage closed processing units for automated steps and isolators to accommodate open manipulations. Some manufacturers of specific modalities, such as adeno-associated virus vectors, are even investigating the possibility of using closed production units to enable continuous processing. Experts speculate this advanced strategy may become standard in the future [24].

Pharma 4.0™ Driven by Robotics and Other Automation Technologies

Robotics and other automation technologies can be leveraged to enable a more intelligent and efficient operation. Process-in-a-box systems that leverage advanced robotic and cobotic technologies to close the ATMP manufacturing process exemplify an overall industry shift toward Pharma 4.0™—that is, an approach to manufacturing that centers on an ecosystem of data-driven, automated, and scalable systems.

For example, process-in-a-box modules can leverage process analytical technology with a feedback loop. A system of advanced sensors enables this approach, allowing the platform to monitor and analyze critical process parameters and critical quality attributes while processing is underway. Robotic mechanisms inside the platform then use this data to make proactive adjustments, often without manual intervention. Capabilities like this help improve batch consistency, maximize uptime, and facilitate transparent and proactive communications with regulators.

Outside of process-in-a-box implementations, the principles of Pharma 4.0™ may lead to improved patient access. By integrating robotics and artificial intelligence, for example, manufacturers can analyze their operational data to optimize their processes and predict potential maintenance needs or material shortages. This foreknowledge can help manufacturers prevent delivery delays or other issues that drive up the cost of final products. These integrations are also key to reliable traceability, a critical factor for cell therapy manufacturers with extensive and complex supply chains and patient-specific workflows.

Decentralized Manufacturing

Decentralized manufacturing can be used to support shorter vein-to-vein timelines and stronger cross-functional partnerships. The strategies described earlier invite ATMP manufacturers to consider their manufacturing models from new perspectives and ask questions that could change how cell and gene therapies are delivered to patients. For example, what if ATMP manufacturers leveraged standardized, robotically driven, user-friendly process-in-a-box systems to move production as close as possible to the patient's bedside?

This vision is driving manufacturers toward decentralized manufacturing for certain cell and gene therapy modalities [25]. The idea is to leverage the mobile and compact nature of closed processing units to untether the manufacturing process from large, centrally located facilities, putting them instead right inside (or adjacent to) hospitals, specialized treatment centers, and other points of care.

Evidence suggests that a distributed manufacturing network supports good patient outcomes by potentially cutting vein-to-vein timelines in half [2]. Regulatory agencies are recognizing the benefit of embracing decentralized manufacturing in some cases; under the Hospital Exemption Clause, for example, the European Medicines Agency authorized local Spanish academic institutions to manufacture CAR T cell therapies outside of the EU's standard centralized marketing authorization pathway [26].

Manufacturers know what they need to get there. When asked in a 2023 industry survey, 500 respondents identified solutions and strategies such as deeper process automation, early regulatory engagement, and alignment with hospital groups as necessary enablers of a decentralized model [27]. Each of these changes will

Figure 4: The pathway to decentralized cell therapy manufacturing [28].

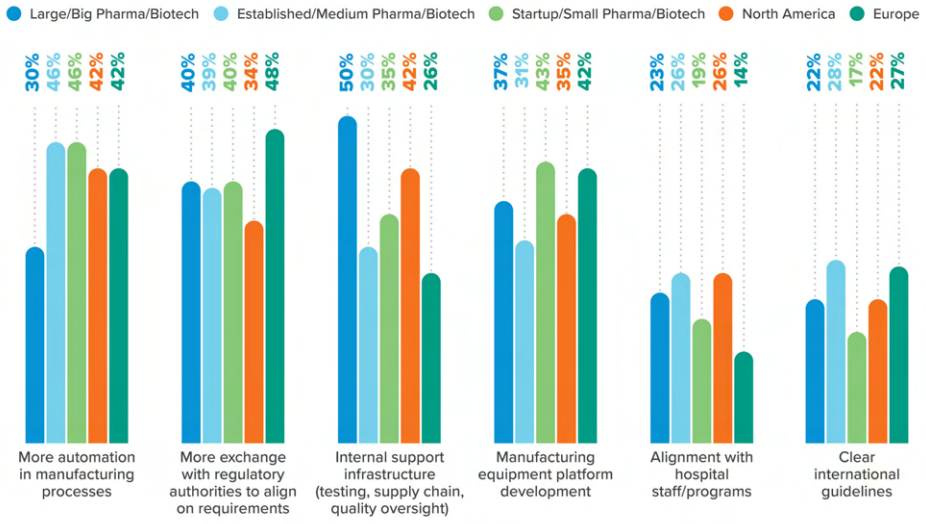
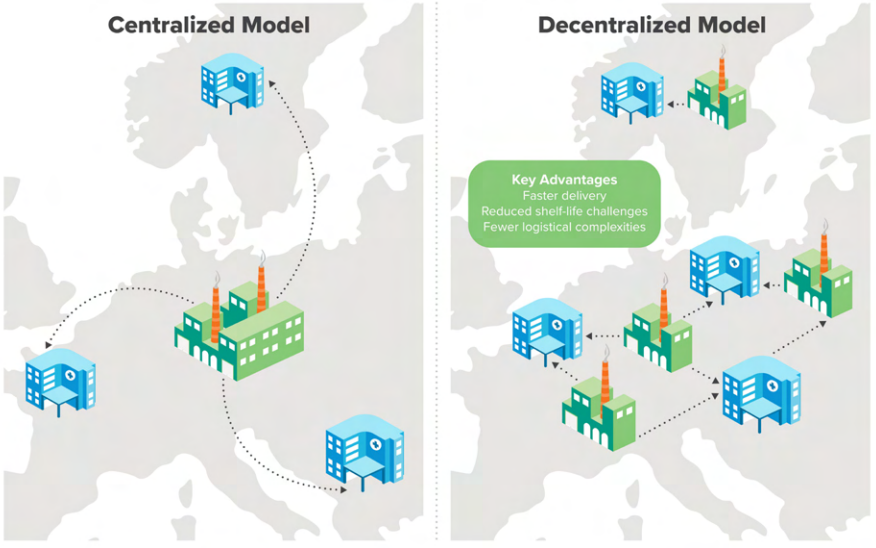


Figure 5: The decentralized manufacturing model.



rely on a commitment to knowledge sharing and co-discovery across the industry.

Just as shared knowledge is an enabler of decentralized ATMP manufacturing, so too is it an outcome. Removing the literal walls between traditional manufacturing sites and patient care sites means that ATMP labs, R&D teams, manufacturers, academic institutions, and hospitals will benefit from less fragmentation and more collaborative problem-solving. At the Medical College of Wisconsin, for example, the Cell Therapy Shared Resource allows researchers and clinicians to work closely together without needing their own GMP manufacturing facilities. Instead, they leverage shared, decentralized cell therapy processing and production infrastructure to manufacture CAR T cell therapies on-site [29].

Applications for this decentralized approach are growing as closed processing technologies continue to evolve. Biotech companies such as Orgenesis are bringing decentralized cell processing to market, with platforms intended to transform the future of ATMP manufacturing [30]. Elsewhere, the collaborative network BioCanRx is currently expanding its decentralized CAR T cell manufacturing capabilities across Canada [31]. Examples like these abound, demonstrating the momentum behind decentralized manufacturing and its potential to shorten timelines, lower manufacturing costs, and improve patient access.

To fully embrace a decentralized model, manufacturers must first address several challenges, including issues related to quality control and concerns about the protection of intellectual property. From a quality perspective, manufacturers have several factors to consider, with solutions available given adequate and early planning.

Regulatory compliance is a chief concern. Ensuring compliance across multiple localized sites requires robust standardized processes supported by a consistent quality management system (QMS). This system should be monitored and enforced via regular audits and compliance checks [32].Establishing a contamination control strategy (CCS) within the framework of that QMS is key. A strong CCS helps manufacturers identify and mitigate high bioburden levels and other quality-related risks, thereby protecting patient safety and ensuring ongoing regulatory compliance [33].

Decentralized manufacturing must also address the potential for variability in local skill sets. The closed and automated technologies described in Section 2 are the key to addressing these risks by minimizing or eliminating the need for human intervention [34]. Supply chain complexity also grows alongside decentralized manufacturing networks. To manage the risk of a supply-related delay, manufacturers need to establish strategic cold chain logistics supported by real-time tracking systems. Finally, integrating data from many localized manufacturing sites into a single main system to monitor for quality and consistency may be a challenge for decentralized manufacturers. Secure cloud-based platforms designed for real-time data exchange are a vital solution [35].

Maintaining integrity around proprietary information is also a chief concern. This is especially true as manufacturers shift from a centrally controlled manufacturing center to a distributed model. In these models, point-of- care institutions are entrusted with some or all elements of the manufacturing process [36].

A strong licensing strategy is one part of the solution. By licensing the production process, manufacturers can ensure that point-of-care institutions, such as teaching hospitals, have the knowledge they need to manufacture ATMPs while proprietary information remains protected. Regular audits are necessary to ensure ongoing compliance with licensing terms [37].

Embedding trained personnel in decentralized manufacturing sites is another useful strategy. These experts can oversee the production process and ensure adherence to protocols (including those designed to protect proprietary information). Using embedded personnel in combination with a system for continuous remote monitoring may help to decrease the risk of security-related compliance issues.

Technology-driven protection measures also have an important role to play in protecting proprietary information within a decentralized manufacturing model. Manufacturers need to implement robust data encryption systems to protect digital information, as well as strict access controls to prevent information leakage [38].

Operational Improvement

Operational improvement (OI) is key in existing or new facilities for streamlined and scalable workflows. A well-designed OI strategy can help ATMP manufacturers understand, troubleshoot, and optimize the unique systems and processes involved in cell and gene therapy production [39]. For manufacturers planning a new commercial-scale ATMP facility, investing in OI during the early design phase will ensure that every capital dollar spent today generates value long into the future. Manufacturers with established facilities can use their OI strategy to proactively identify and eliminate issues before they happen and maximize the performance of their existing systems.

Robust OI studies rely on several advanced tools, each contributing to long-term process optimization. The digital twin is a virtual duplication or computational model of a specific manufacturing process or the facility as a whole. Using that digital twin, ATMP manufacturers can leverage modeling and simulation to troubleshoot performance issues (in an existing facility) or test scenarios before committing to a facility layout or investing in new equipment.

Process monitoring models can direct manufacturers toward emerging trends and improvements that will reduce out-of-specification events and avoid conformance issues. Discrete event simulations go even further, allowing manufacturers to incorporate uncertainty into their simulations. This is an especially useful tool for ATMP manufacturers, who face uncertainty on multiple levels, from sudden shifts in demand that make capacity alignment difficult to transport issues that delay the start of new batches.

Manufacturers can use these OI tools to continuously evaluate and address issues that impact the duration, complexity, and reliability of the ATMP production process. For example, simulations can help establish an equipment utilization strategy that balances efficiency with the need for risk-based redundancy planning to avoid bottlenecks or unplanned downtime. These tools are also vital in scheduling maintenance and cleaning activities, optimizing staffing strategies, streamlining the flow of personnel through the facility, increasing warehouse and storage efficiencies, optimizing quality control testing protocols, and much more.

CONCLUSION

Knowledge sharing is the key to accelerating ATMP research, broadening patient access, and reducing costs. The ATMP industry can overcome the challenges it faces by removing silos within the scientific community and inviting a meaningful exchange of knowledge and insight between academic research bodies, manufacturers, equipment suppliers, regulatory agencies, and public healthcare institutions. Already, examples of research breakthroughs accelerated by collaboration abound.

Developers of cutting-edge manufacturing technologies are working closely with cell and gene therapy research and development accelerators, each intent on improving patient access through novel strategies and solutions, such as process-in-a-box technologies [40, 41]. Collaborations like these are the key to unlocking the full promise of ATMPs. Only by sharing ideas and working together

to develop simpler, more flexible, and less costly manufacturing pathways can ATMP manufacturers ensure access to high-quality cell and gene therapies for every patient in need.

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RESILIENCE FOR CELL THERAPY MANUFACTURERS: Five Strategies

By Maddie Lawhorn and Peter Walters

For patients who depend on personalized medicine, turnaround time matters. However, moving quickly is difficult for cell therapy companies because designing personalized therapies presents unique challenges unknown in traditional biotechnology. In this article, we'll examine five strategies to help cell therapy companies develop resilience against these challenges, positioning themselves to reliably deliver what patients need.

Personalized cell therapies use a patient's own cells (autologous) or donor cells (allogeneic) to treat diseases in ways that traditional off-the-shelf biologics cannot. To deliver on that promise, manufacturers of these novel therapies must navigate a complex, individualized product cycle, starting with cell collection from the patient and moving through processing, cell selection, possible cell modification, expansion, and quality testing steps before finally delivering the finished therapy back to the same patient. Each of these steps must happen quickly, reliably, and without interruption to meet the patient's need for urgent intervention. The criticality of this manufacturing cycle requires a comprehensive cell therapy manufacturing resilience strategy.

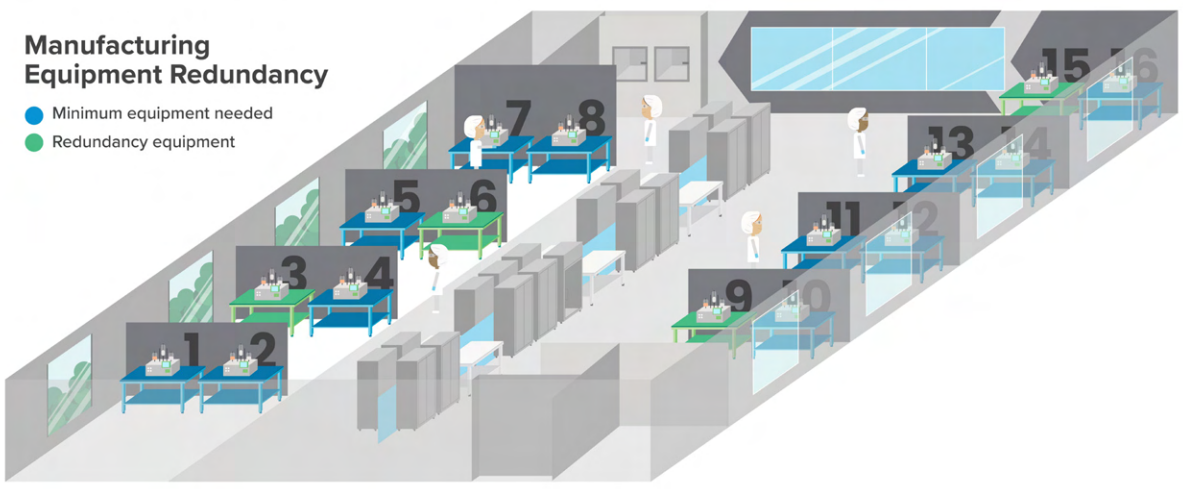
KEY CONSIDERATIONS

Manufacturers of all drug types can benefit from improved resilience, but the stakes are elevated in the field of cell therapy. Here's why:

- The consequences of a lost batch could be life or death. Manufacturers of traditional drug products can safeguard against a product shortfall by building an inventory of contingency stock. However, that is not an option for manufacturers of autologous cell therapies because they must produce batches in real time to meet a specific and urgent patient need. If a batch is underway, that means a critically ill patient needs it. Losing that batch is simply not an option.
- Turnaround time is vital. Reducing vein-to-vein turnaround time has the potential to extend patient lives. One recent study, for example, correlated that cutting the turnaround time of chimeric antigen receptor (CAR) T cell therapies from 54 to 24 days could extend patient life expectancy by 3.2 years [1]. Faster delivery may also be a market differentiator for manufacturers, and some may commit to their runtime as part of their regulatory filing. For these reasons, maintaining a predictable turnaround time, safe from unexpected disruptions or delays, is vital.
- Consistency is a challenge. Cell therapy manufacturers rely on living cells as their starting material, derived from a donor or, in the case of autologous cell therapies, from a patient facing a serious illness. Producing a therapeutic vehicle from living cells is a complex challenge. Manufacturers are continuously evolving their approaches and platforms to find potential solutions for that challenge. With few technological solutions on the market capable of handling that development variability, many manufacturers must rely on manual processing steps. This makes it difficult to deliver high-quality and consistent therapies at scale.
- Cell therapies require a different manufacturing philosophy. When expanding large volumes of in-process material, manufacturers of traditional biologics can benefit from the economics of scaling up by using larger bioreactors or production systems to increase batch volumes [2]. Cell therapy manufacturers do not have such an advantage. They produce very small batches—sometimes as small as a single patient, in the case of autologous cell therapies. That means they must scale out by adding more production units of the same size to work in parallel [3].

Resilience is the key to overcoming these challenges. Resilient manufacturers know where they are vulnerable to delays or

Figure 1: Equipment-level redundancy in a cell therapy manufacturing facility.



downtime, and they have a complex arsenal of strategies for managing that risk. In this article, we'll look closely at five of those strategies. Among the many interrelated approaches that manufacturers rely on to keep operations running and ensure patients receive needed therapies, these five are especially critical: redundancy, maintenance, automation, segregation, and regulatory compliance.

REDUNDANCY

Equipment Redundancy

Owners must weigh the capital and operational costs of installing and maintaining redundant equipment against the business risks of an unexpected interruption.

In a traditional biotech facility

Manufacturing capacity is tied in part to bioreactor productivity. If a production reactor goes offline, that capacity is significantly hindered. Addressing that risk by installing, calibrating, and maintaining an additional "production-ready" bioreactor is an option—but that would mean investing significant capital, time, and footprint in idle equipment. And even if a manufacturer chooses to make that investment, their production system is still vulnerable to resilience issues. What if a system in the seed train goes offline, for example? For these reasons, traditional biotech manufacturers typically build resiliency through other strategies discussed next, rather than focusing on equipment-level redundancy.

In a cell therapy facility

By contrast, equipment redundancy in a cell therapy manufacturing facility is easier to rationalize. The window of opportunity to successfully treat critically ill patients is often very brief; manufacturers are therefore driven to avoid unexpected downtime by investing in redundant equipment. Given the relatively small size of that equipment, installing and maintaining it is easier to justify from a cost perspective than the large-volume systems used in traditional biotech (see Figure 1).

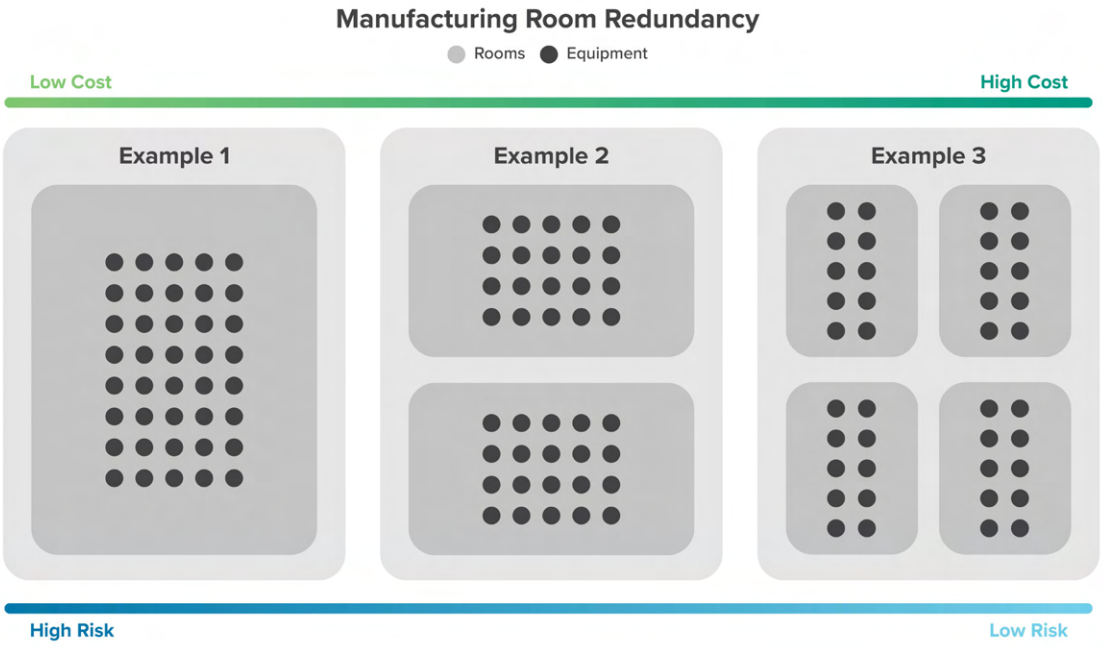
Also, cell therapy equipment is often highly versatile. An automated, closed cell processing unit may support multiple manufacturing steps from cell isolation through transduction and expansion, with programmable options to improve versatility [4]. Flexible platforms like this can help cell therapy manufacturers improve the cost effectiveness of their equipment redundancy investments.

It is also important to note that equipment redundancy does not always mean carrying idle systems. Because cell therapy manufacturers must scale out, they have an opportunity to build redundancy into their utilization strategy. For example, a cell therapy manufacturer who requires 12 production systems to meet their throughput target might choose to purchase and install 16 systems, thus building a 25% margin into their utilization rate. All systems will be used, just to a lesser extent. This strategy addresses another important consideration in the cell therapy submarket: cost of goods and its impact on patient access. By balancing equipment failure risk with idle capacity, manufacturers can both establish resilience and manage their capital expenses, which in turn could contribute to better assurances for patients.

Room Redundancy

In any facility, several threats could impact the cleanliness of a production room. A mechanical or electrical failure could cause the room's air handler or high efficiency particulate air filter to fail. Environmental sensors could detect particles or viables as a result of inadequate cleaning or operational activities. A production spill could both compromise cleanliness and expose in-process

Figure 2: Room redundancy in a cell therapy manufacturing facility.



materials to cross-contamination. Personnel are widely understood as a significant source of microbial contamination [5], with improper gowning or poorly applied aseptic techniques increasing the risk of environmental monitoring excursions.

Manufacturers can mitigate these risks with rigorous gowning validation, restricted flow of personnel, and continuous monitoring of cleanroom conditions, but the risk that a production room may be compromised remains. To restore it, manufacturers of all types must address the root cause of that event with repairs or remediation, then clean the room appropriately. Depending on the severity of the event, all in-process batches must be either discarded or flagged for quarantine and evaluation by Quality Assurance.

In a traditional biotech facility

Manufacturers carry and manage the risk of a compromised production room. An N+1 strategy in which manufacturers support critical systems with a backup system may offer some protection. However, maintaining entire redundant cleanrooms is not justifiable for the same reasons that rule out equipment redundancy in most cases: the expense outweighs the business risks.

In a cell therapy facility

Cell therapy manufacturers should approach this risk differently, with consideration for the particle concentration permitted for each cleanroom classification, as defined in "Annex 1: Manufacture of Sterile Medicinal Products" [6]. For a facility attempting to embrace process closure, the quantity of Grade B suites needed (for open process steps) is often based on how many vectors a manufacturer plans to use or how many Grade C suite activities need support (for closed process steps).

During normal operation, Grade B suites are typically dedicated to a specific product or vector. However, if another suite goes down, a Grade B suite can be leveraged agnostically (following proper cleaning and room turnover protocols). Therefore, manufacturers may benefit from maintaining a single redundant Grade B suite or ensuring that their Grade B suite capacity is sufficient to support normal operations should one such suite be unexpectedly deployed for another purpose.

Grade C suites, where most closed processing activities in a cell therapy manufacturing facility occur, present a different opportunity. Because they operate a large number of small, redundant production systems, manufacturers can put all systems in a single room or distribute them across multiple rooms, depending on their business risk profile (see Figure 2).

For example, a manufacturer with 40 manufacturing systems may follow the model laid out by traditional biotech facilities, locating all 40 in the same room. Alternatively, they may use two rooms and put 20 systems in each one or use four rooms housing 10 systems each. More rooms mean higher costs—more airlocks, greater facility footprint, more rooms to environmental monitoring (EM) sample, possibly more heating, ventilation, and air conditioning (HVAC) complexity and equipment, etc.—but it also means a lower risk that multiple batches will be compromised by the same room-based contamination event. Manufacturers

should consider their business risk profile when weighing these benefits and trade-offs to arrive at a room redundancy strategy that is appropriate for their situation.

Support System and Nonproduction Area Redundancy

In a traditional biotech facility

When access to a facility-based support system is critical, and the costs are justifiable, traditional manufacturers may choose to duplicate that full system. More often, though, they will focus their redundancy strategy on critical subsystems and their component parts. Rather than invest in a redundant water for injection generation system, for example, owners may choose to maintain an inventory of redundant supply pumps.

In a cell therapy facility

For cell therapy manufacturers, this redundancy strategy must go even further. Facility corridors, for example, are vital arteries that keep all processes moving forward. What happens if a contamination event or a failing air handler compromises such a corridor? Without access to the production suites, operators would not be able to perform time-sensitive manual steps on in-process materials. Production would come to a standstill, potentially putting multiple batches at risk. In most scenarios, adding a redundant supply corridor would be impractical. Instead, cell therapy manufacturers should rely on backup air handling units, over-containing protection systems, spill containment protocols, and other contingency measures to proactively eliminate the possibility of a contamination event in the first place.

Power Supply Redundancy

In a traditional biotech facility

To ensure uninterrupted access to power, traditional manufacturers may rely on many layers of redundancy. Sourcing power from separate municipal grids or substations can reduce the risk of an outage; if an outage does occur, battery banks and automated generators can provide short-term backup power to HVAC systems, freezers, and other critical equipment. In addition to these backup systems, traditional manufacturers may also rely on a small uninterruptible power supply (UPS) unit to maintain uptime for their computer control systems.

In a cell therapy facility

Cell therapy manufacturers should approach this risk with a different philosophy. To avoid the possibility of any electrical interruption, many will rely on a larger UPS to support the majority of their manufacturing systems. This impacts the way cell therapy manufacturers design their overall electrical systems. Some invest in photovoltaic panels and other sustainable technologies to generate and store a limited amount of on-site power, with generators on hand to fill the gap. In addition to its decarbonization benefits, this strategy partially untethers manufacturers from vulnerable municipal infrastructure, ensuring facility wide uptime even in the event of an outage.

In a resilient manufacturing facility, processing happens efficiently, unplanned downtime is rare, and final products reach patients rapidly and safely. For cell therapy manufacturers, achieving that vision is imperative: lives depend on it.

MAINTENANCE

In a Traditional Biotech Facility

Resilient facilities of all types rely on preventive maintenance to help identify and eliminate issues before they happen. Traditional manufacturers typically achieve this through planned facility shutdowns, giving maintenance teams a service window of several days or weeks. To de-risk this strategy from a business perspective and prevent shortages in the market during a planned shutdown, manufacturers often draw from inventory stockpiled for that purpose.

In a Cell Therapy Facility

This strategy does not translate well to the cell therapy manufacturing context, where a planned shutdown is more than a business risk—some companies see it as an ethical and moral issue, with patient lives at stake. Personalized medicine cannot be stockpiled, and patients cannot wait for treatment while facility systems undergo maintenance.

The solution is often a strategy of rolling shutdowns, which work hand-in-hand with the redundancy planning described previously. Through careful production planning supported by detailed workflow and schedule mapping, cell therapy manufacturers can pause operations in one area of the facility to perform critical tasks (e.g., Grade B suites require aseptic process simulations twice a year [7], which may identify maintenance interventions required to proactively guard against contamination). Meanwhile, the equipment and room redundancy strategies described earlier ensure that production may continue elsewhere, uninterrupted.

In areas where redundancy is difficult or impossible to achieve (such as in supply corridors), redundant mechanical infrastructure is key—shut down one system for maintenance, keep the other one active for ongoing environmental support. This strategy ensures that all critical infrastructure receives regular preventive maintenance without the need for a full-system shutdown.

However, even the most robust predictive or preventive strategies cannot rule out the possibility of unplanned maintenance. Systems may unexpectedly break, malfunction, or fall out of calibration. To accelerate recovery in such cases, cell therapy manufacturers can rely in part on rented equipment to address specific temporary issues (e.g., compressed gas or liquid nitrogen dewars for malfunctioning utility supply systems). For this strategy to work without causing unexpected delays, manufacturers must have a plan in place to accelerate the qualification process for rented equipment. Preestablished vendor agreements, standardized validation protocols, and preapprovals for certain equipment may play a role.

Manufacturers should also establish a tiered on-site redundancy strategy. Redundant online systems represent the highest tier; these systems are online, in-room, and ready to use. Redundant systems that are stored elsewhere (e.g., in the warehouse) represent the next tier; these systems require installation and some light management but getting them up and running requires less time than repairing the existing system. At the lowest level parts and equipment are stored in the warehouse to facilitate repairs. This tier closely resembles the strategy typically used in large biotech facilities. Cell therapy manufacturers may rely on this tier to support their most expensive and complex systems, such as filling line isolators or autoclaves.

AUTOMATION

In a Traditional Biotech Facility

As a pillar of the Pharma 4.0™ evolution [8], automation can enhance manufacturing resilience by reducing operator-driven steps and feeding proactive risk-management strategies with high-quality, real-time data. Traditional biotech facilities meet many of the conditions that make such automation implementations effective and scalable. For one thing, they typically feature standardized processes, making it possible to integrate automation platforms rapidly and effectively. The volume of in-process materials moving through production at any given time also enables an automation-focused manufacturing philosophy. When moving thousands of liters of in-process solution at a time, for example, some degree of process loss during an automated bulk transfer may be acceptable.

In a Cell Therapy Facility

The comparatively small volumes of in-process materials, as well as the manual nature of many cell therapy manufacturing processes, make it difficult for operators in this submarket to leverage the full potential of automated systems at scale. That will change as automation technology evolves—already, the market offers several automated platforms that aim to meet the unique needs of the cell therapy manufacturing life cycle [9]. By embracing automated technologies, manufacturers can eliminate manual tasks prone to human variation and replace them with consistent and standardized platforms. This will improve reproducibility and open the door to point-of-care manufacturing, which may translate to lower costs and faster access for patients [10].

However, to move into this future of automated cell therapy production, manufacturers must first overcome several challenges. Working with patient cells as a starting material, for example, means accommodating a degree of variability and unpredictable fluctuations [11], which can be difficult to do using automated systems.

Another challenge: many currently available automated technologies are not yet capable of performing the delicate maneuvers required to prevent process holdup loss. Losing even small volumes during a critical transfer (that must be accounted for) could have far-reaching effects on the cost and reproducibility of the final cell therapy product. Estimated material costs for cell therapy manufacturers average about 36% of their overall manufacturing cost of goods, with some manufacturers reporting as high as 70% [12]. Material line losses could create a financial impact, which could translate to consequences for patients,

whose lives may depend on insurance access to these already expensive therapies.

Although automation is a key to resilient and cost-efficient manufacturing, these challenges have put the widespread adoption of scalable, automated solutions just out of reach for many cell therapy manufacturers—at least for now. New opportunities to bring automation into the cell therapy facility are emerging all the time, thanks to an increasing number of manufacturers in this submarket who are working in partnership with equipment vendors to develop solutions that work for this unique context [13].

SEGREGATION

Cleanroom segregation is a critical element of contamination control and operational efficiency. A segregated cleanroom leverages physical and procedural design elements to prevent cross-contamination and ensure that a failure in one processing suite does not impact other production areas, based on a thorough risk assessment [14]. This falls within a facility's contamination control strategy (CCS), which defines the protocols in place to prevent the contamination of sterile or aseptic processes [15]. By establishing a robust CCS and supporting it with appropriate segregation, manufacturers can improve their resilience against unexpected downtime or lost throughput.

However, segregation can sometimes work against the goal of operational efficiency. For example, physically separating previral and post-viral processes in monoclonal antibody manufacturing may increase resilience against contamination risks, but this type of room-based segregation will limit efficiencies, drive up both the size of the facility and its cost to operate, and reduce overall manufacturing flexibility. The key is to keep both priorities in balance.

In a Traditional Biotech Facility

Traditional biotech manufacturers have a big advantage when it comes to maintaining that balance: they can leverage process closure technologies to push segregation to the equipment level rather than relying on room classifications and environmental segregation to prevent contamination. This can open the door to a simpler, more scalable, and more cost-effective facility layout, such as a ballroom design in which multiple processes are completed in parallel, with mobile equipment that can be reconfigured as needed [16].

In a Cell Therapy Facility

Cell therapy manufacturers should think about this calculation differently. As established in the preceding section, full end-to-end process automation at the equipment level can be difficult to implement. As a result, many manufacturers are tethered to a room-level segregation strategy, depending on the degree of automation and process closure they are able to leverage. From an efficiency perspective, this can make it difficult to optimize the cell therapy facility.

The complexity of scaling out rather than up adds to this challenge. As discussed in the section about room redundancy, processing potentially hundreds of small batches in a single shared cleanroom would generate a high degree of efficiency. However, a single HVAC issue could compromise every batch. Distributing these batches across multiple rooms lowers that risk but may increase the facility's footprint and drive up both capital and operational expenses, considering that every additional room would require manufacturers to replicate and scale out all room-based functionalities (e.g., airlocks, in-process testing stations, staffing plans, such as supervisors, EM sample locations, and so on).

Given these choices, how can cell therapy manufacturers balance segregation and efficiency to support ongoing resilience? The answer will involve some degree of risk-based redundancy, calculated function by function, to ensure continuity of operations in the event of a contamination event. Broadly speaking, manufacturers should consider at least some degree of segregation at the room level, depending on how many batches product types they intend to manufacture concurrently.

REGULATORY COMPLIANCE

For any manufacturer of a drug product carrying a sterile claim, supporting that claim with appropriate facility and process designs is a critical priority. It is the key to ensuring patient safety and maintaining compliance with relevant guidelines.

In a Traditional Biotech Facility

Traditional biotech manufacturers typically apply a sterile filtration step to remove microorganisms and particulates from final product formulations. Downstream of the sterile filter, they must comply with "Annex 1: Manufacture of Sterile Medicinal Products" [17] and the "Guide to GMP for Medicinal Products" [18]. Although Annex is not formally adopted by the US Food and Drug Administration (FDA), US-based manufacturers generally choose to follow the guideline's principles to ensure patient safety and compete on a global scale.

Upstream of the sterile boundary, manufacturers comply with "Annex 2: Manufacture of Biological Active Substances and Medicinal Products for Human Use" [19] aiming to control bulk drug bioburden levels. Efficient measures like process closure, robust cleaning protocols, and ongoing monitoring and validation help maintain low microbial loads as bulk drugs move toward sterile filtration and downstream aseptic processing.

In a Cell Therapy Facility

Compliance is more complicated within the context of cell therapy. In 2017, the European Commission published EudraLex Volume 4, Part IV "Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products" [20]. Four years later, the Pharmaceutical Inspection Co-Operation Scheme revised its "Guide to Good Manufacturing Practice for Medicinal Products" annexes to include Annex 2A, "Manufacture of Advanced Therapy Medicinal Products for Human Use" [18].

Regulatory updates provide cell therapy manufacturers with a set of GMP guidelines dedicated to their manufacturing context. Although Annex 1 is not strictly mandated by Part IV, many cell therapy manufacturers aim to align with Annex 1 principles. Achieving alignment can be challenging in cell therapy. Sterile filtration is not possible for the process stream, given that pore size in sterilizing-grade filters is 0.2/0.22 µm [21] and typical human cells are 25 µm [22]. As a result, the whole manufacturing cycle might have to be performed aseptically. To achieve this, cell therapy manufacturers must rely on their evidence-based quality risk-management program to identify and redress contamination vulnerabilities at any point in production [23].

A CCS can help cell therapy manufacturers achieve this aim [15]. Although it is not required, US-based cell therapy manufacturers may use a CCS as a signal to regulators of their robust commitment to identifying and addressing potential contamination risks across the cell therapy life cycle. The CCS encompasses many of the elements discussed throughout this article, as well as components such as cleanroom classification, cleaning regimes, pressurization schemes, gowning practices, and more. It is fundamental to establishing a resilient cell therapy manufacturing strategy that protects critical in-process solutions from the possibility of contamination.

CONCLUSION

In a resilient manufacturing facility, processing happens efficiently, unplanned downtime is rare, and final products reach patients rapidly and safely. For cell therapy manufacturers, achieving that vision is imperative: lives depend on it. But it is also uniquely difficult. To get there, cell therapy manufacturers must learn and diverge from traditional biotechnology manufacturers, ultimately building a strategy for resilience that centers on the patient and their time-sensitive need for high-quality, life-saving personalized therapies.

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APPLICABILITY OF VAPORIZED HYDROGEN PEROXIDE

for Contamination Control of Lyophilized Biohazards

By Birte R. Scharf, PhD, Maximilian Ferdinand Eizinger, PhD, Maren Saade, Andrea Hawe, PhD, Tim Menzen, PhD and Hussein Bachir, PhD

Controlling contamination in environments where biological medicinal products are handled is of paramount importance to ensure the safety of personnel, sterility of drug products, and protection of the surrounding environment. The application of vaporized hydrogen peroxide (vH_2O_2) has emerged as a promising method for postproduction decontamination due to its ability to degrade biohazards into nontoxic byproducts.

The majority of biologics and advanced therapy medicinal products (ATMPs) are parenterals that must be filled aseptically to maintain structural integrity and therapeutic efficacy, because terminal sterilization is not possible due to the instability of the product. Therefore, filling is often performed in isolators to ensure drug product quality and safety. Due to their sensitivity, biologics are often freeze-dried to increase product stability and shelf life.

This study explores the efficacy of vH_2O_2 decontamination for lyophilized biologics and ATMPs, considering the expected challenges for lyophilized drug products. We conducted experiments to investigate the influence of lyophilization and formulation composition, by using pharmaceutically relevant matrices, on the efficacy of vH_2O_2 decontamination. Our study highlights the difficulties in decontaminating lyophilized drug products in different pharmaceutically relevant matrices and proposes an isolator design solution to mitigate these challenges.

INTRODUCTION:

Biologics and ATMPs—which include proteins, peptides, antibodies, vaccines, active viruses, and viral vectors, constitute a significant element of approved medical treatments and ongoing clinical trials. Until now, most biologic drug products were designed and destined for the parenteral route of administration. In most cases, aseptic filling is required to retain their structural integrity and therapeutic efficacy, instead of terminal sterilization, which would lead to severe degradation of the sensitive molecules [1].

Handling genetically modified microorganism-based biologics and ATMPs can pose biohazardous risks to humans and the environment, and requires handling under the appropriate biosafety level. Contamination control in environments where these potentially hazardous biologics and ATMPs are handled is crucial to prevent accidental releases of the microorganisms to the environment and ensure product quality. Furthermore, cross-contamination is a central concern in filling suites for biologics and ATMPs, especially given the smaller batch sizes and diverse products being processed. Within the aseptic filling process, isolators play a vital role in maintaining product integrity and ensuring personnel and environmental safety [2].

The use of vH_2O_2 is a well-established approach for decontamination of surfaces due to its ability to destroy a wide range of microorganisms, including viruses and spores [3, 4]. Therefore, it is also used for postproduction decontamination of isolators, restricted access barrier systems (RABS), and freeze dryers to eliminate any potential sources of contamination that may have arisen during the manufacturing process [5]. To encourage ethylene oxide sterilization alternatives, the US Food and Drug

Administration (FDA) recently categorized vH_2O_2 as a category A method of sterilization for medical devices [6]. In Germany, the Association for Applied Hygiene (VAH) approved vH_2O_2 as a disinfectant, but exclusively for the decontamination of visually clean surfaces [7].

All biopharmaceuticals are susceptible to degradation due to their macromolecular complexity and sensitivity to environmental conditions (e.g., temperature, pH, light). Particularly viruses, which can be used as vectors in ATMPs as well as live vaccines, pose biohazard risk (biosafety level ≥ 1) [8–10]. Moreover, viruses are susceptible to water-mediated destabilization and degradation pathways above 8°C. Typically removal of bulk water significantly increases the stability of viruses. Thus, most of the virus-based vaccines are freeze-dried drug products [11].

For product and operator protection, the entire filling and lyophilization process of (genetically modified) microorganism-based biologics and ATMPs must be executed under aseptic conditions. During these processes, there are multiple critical steps identified that could cause a contamination of he vial surfaces and isolator chamber with free-dried, biohazardous drug product material.

This article presents the results of experimental studies conducted to investigate the vH_2O_2 decontamination efficacy of lyophilized *Geobacillus stearothermophilus* spores in the dependence of different pharmaceutically relevant matrices. Based on these results, it can be concluded whether decontamination with vH_2O_2 is applicable as postproduction decontamination of biohazardous, lyophilized biologicals and ATMPs, or whether additional requirements need to be placed on the design of the barrier system.

EXPERIMENTAL DESIGN AND RESULTS

For the semiquantitative determination of the decontamination efficacy of a vaporized 35% aqueous hydrogen peroxide solution, 2×10^6 *Geobacillus stearothermophilus* spores, which represents a respected bioindicator (BI) for the process validation of vH_2O_2 decontamination, were diluted in a 300 µL matrix. In total, four different pharmaceutically relevant aqueous matrices were used (see Table 1) to investigate the impact of the formulation composition and resulting lyophilized cake on the vH_2O_2 decontamination efficacy.

To assess the influence of the dry cake on the vH_2O_2 decontamination, efficacy samples were either freeze-dried in a pilot-scale freeze-dryer (Epsilon 2-4 LSCplus, Martin Christ Gefriertrocknungsanlagen GmbH, Osterode, Germany) (see Table 2 and Table 3 for freeze-drying protocol), or heat-dried in a drying cabinet (UFP 550, Memmert GmbH + Co. KG, Schwabach, Germany) at 60°C for 24 hours.

After successful lyophilization, the different formulations resulted in dry cakes with structural and physical heterogeneity. Spores diluted in water only (control) did not form a visible cake, due to the lack of bulking agents. Based on the amorphous disaccharide sucrose content in FB1 and FB3, formulations 1 and 3 lead to amorphous lyophilized cakes after drying. In contrast, the ratio of four parts crystalline mannitol and one part amorphous sucrose in FB2 is expected to form a crystalline lyophilized cake [12].

Heat-dried samples did obviously not result in a lyophilized cake, but formed a thin layer at the bottom of the vials because of collapse when drying is performed at high temperature. Heat-dried and freeze-dried samples were exposed to vH_2O_2 gasing cycle for up to 60 minutes. Photos of the dried units are depicted in Figures 1A–1H. The amplification of *Geobacillus stearothermophilus* was

Table 1: Composition of the different matrices used in the study.

#	Matrix
Control	Water
FB1	5% sucrose
FB2	20 mM histidine-HCl, pH 6.5, 4% mannitol,
FB3	1% sucrose
	20 mM histidine-HCl, pH 6.5, 1 mM magnesium chloride ($MgCl_2$), 35 mM sodium chloride (NaCl), 7% sucrose, polysorbate 80 (0.02%)

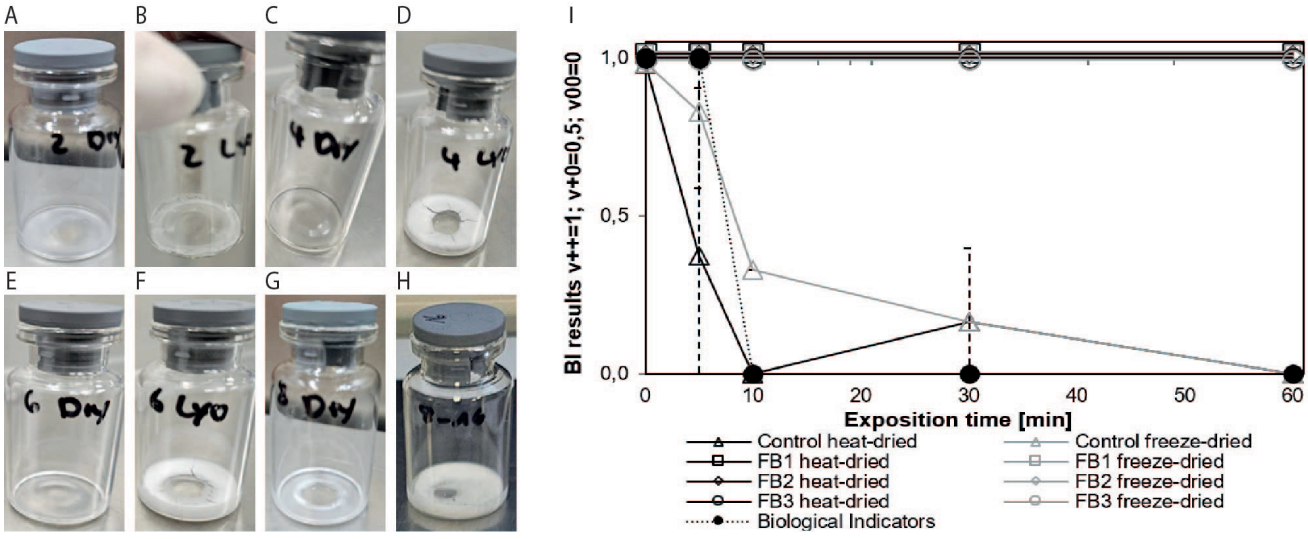
Table 2: Freeze-drying recipe for control and FB1 samples.

Step	Shelf Temperature [°C]	Time [hh:mm]	Vacuum [mbar]	Safety Pressure [mbar]
Loading	20	-	-	-
Freezing	-45	01:05	-	-
Freezing	-45	02:00	-	-
Main Drying	-45	00:01	0.180	-
Main Drying	-23	00:20	0.180	0.77
Main Drying	-23	26:00	0.180	0.77
Main Drying	-23	00:01	0.05	-
Final Drying	20	00:20	0.05	-
Final Drying	20	07:30	0.05	-

Table 3: Freeze-drying recipe for FB2 and FB3.

Step	Shelf Temperature [°C]	Time [hh:mm]	Vacuum [mbar]	Safety Pressure [mbar]
Loading	20	-	-	-
Freezing	5	00:15	-	-
Freezing	5	01:00	-	-
Freezing	-40	01:30	-	-
Freezing	-40	04:00	-	-
Main Drying	-40	00:06	0.133	off
Main Drying	-10	01:30	0.133	0.26
Main Drying	-10	20:00	0.133	0.26
Final Drying	20	02:30	0.133	0.26
Final Drying	20	06:00	0.133	0.26

Figure 1: Spores in the four different formulations: (1A) control heat-dried and (1B) freeze-dried; (1C) FB1 heat-dried and (1D) freeze-dried; (1E) FB2 heat-dried and (1F) freeze-dried; (1G) FB3 heat-dried and (1H) freeze-dried. Heat-dried and freeze-dried samples were exposed to vH2O2 gassing cycle for up to 60 min. The amplification of *Geobacillus stearothermophilus* was evaluated after an incubation period of 7 days (I).



v++: amplification rate according to turbidity of tryptic soy broth (TSB) is equal to positive control, v+0: reduced amplification rate according to turbidity of TSB compared to positive control, v00: amplification rate according to turbidity of TSB is equal to negative control. N = 2 with n = 3 per formulation.

evaluated after an incubation period of seven days (see Figure 1I).

In the proof-of-concept pre-test, *Geobacillus stearothermophilus* spores diluted in water were tested to determine if they could still replicate after undergoing heat-drying, respectively, the lyophilization. In addition, it was examined if vH_2O_2 could distribute within the 6R vials in sufficient quantity and in less than 10 minutes to inactivate the *Geobacillus stearothermophilus* spores. The usual gassing time for a chamber of this size is approximately 20 minutes for inactivation of BIs at all challenge locations and 5–10 minutes for inactivation of BIs at the location where the samples were actually placed in this experiment setting.

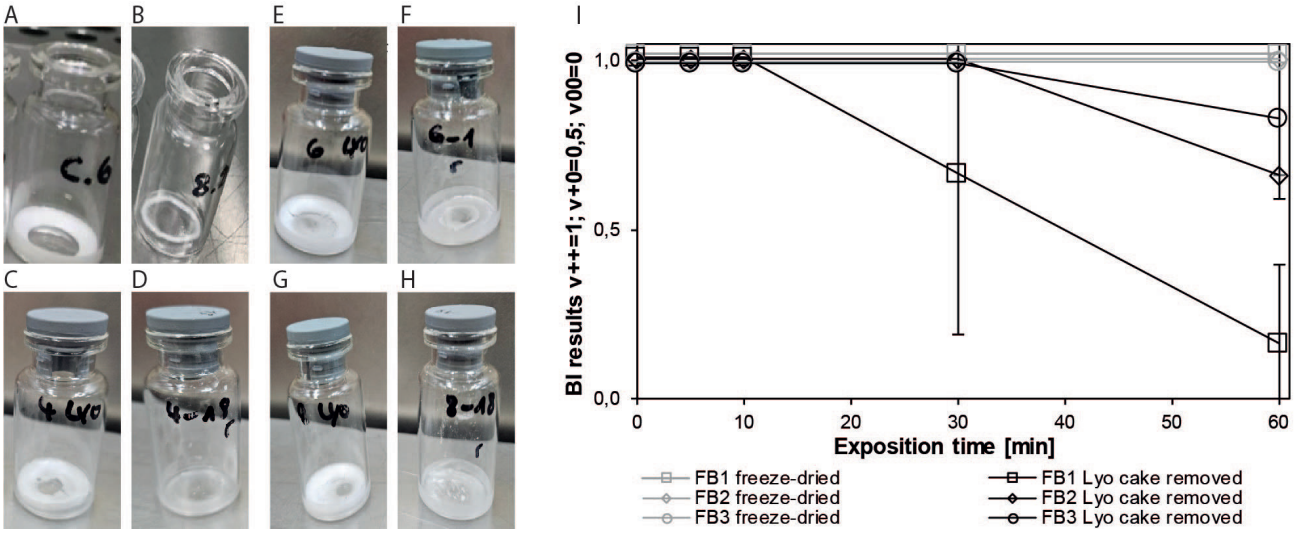
As a control, the commercial biological indicator carriers (Mesa Labs, 1.9106 spores per carrier) were added in 6R vials and underwent the same vH_2O_2 gassing cycle. After the gassing cycle, the vials were filled with 6-millimeter (mL) TSB growth media and incubated at 57.5°C for seven days. Vials without any BI, filled with TSB only, served as negative control. To evaluate the amplification of *Geobacillus stearothermophilus* in TSB, the turbidity of the samples was compared with the turbidity of the negative control (TSB only) and the positive control (non-vH_2O_2 treated BI in TSB).

The first evaluation of growth was performed after 16 hours, and the final evaluation after 7 days. The non-vH_2O_2 treated lyophilized and heat-dried bacteria exhibited a similar growth kinetic as the commercial bioindicator (data not shown), thus neither the heat-drying nor the freeze-drying of the spores in water affected the viability of the spores. Furthermore, it was demonstrated that the commercial biological indicators in vials, heat-dried spores, and freeze-dried spores exhibit similar vH_2O_2 inactivation time in this pre-test (data not shown). These findings were essential to perform the next experiments.

Next, the impact of the matrix on the vH_2O_2 inactivation of freeze-dried and heat-dried *Geobacillus stearothermophilus* samples was evaluated. Therefore, the freeze-dried and heat-dried samples were subjected to the vH_2O_2 cycle for 5, 10, 30, and 60 minutes. The biological indicators, the lyophilized spores and heat-dried spores in water, for which no solid cake was formed, were inactivated after 60 min vH_2O_2 gassing. In contrast, the *Geobacillus stearothermophilus* spores in the other matrices, embedded in the dried matrices, still exhibited bacterial growth, therefore were not inactivated after 60 minutes of vH_2O_2 treatment, regardless of heat-dried or freeze-dried (see Figure 1I).

Subsequently, the effect of the lyophilized cake surface and thickness on the vH_2O_2 decontamination efficacy was evaluated using the FB1 formulation (pre-study "lyo cake"). Therefore, an intact FB1 lyophilized cake was crushed and mostly removed from the vial, leaving only a thin dust layer of the *Geobacillus stearothermophilus* containing lyophilized cake on the inner surface of the glass vial. In contrast to the intact FB1 lyophilized cake, which was partially dissolved after the vH_2O_2 gassing cycle (Figures 2A and 2B) and where the spores could not be inactivated even after 60 minutes, the thin lyophilized cake dust layer containing *Geobacillus stearothermophilus* exhibited a reduced bacterial growth rate after

Figure 2: Vials containing FB1 lyophilized cake (2A) before and (2B) after a 48-minute vH_2O_2 gassing. Vials with intact lyophilized cakes and vials with lyophilized cake dust layer remains of (2C and 2D) FB1, (2E and 2F) FB2, and (2G and 2H) FB3. Comparison of vH_2O_2 inactivation time and efficacy of intact lyophilized cakes and lyophilized cake dust layers (lyophilized cake removed). The amplification of Geobacillus stearothermophilus was evaluated after incubation for seven days (2I).



v++: amplification rate according to turbidity of TSB is equal to positive control; v+0: reduced amplification rate according to turbidity of TSB compared to positive control; v00: amplification rate according to turbidity of TSB is equal to negative control. N = 2 with n = 3 per formulation.

Integrated return air filters located directly at the main isolator chamber pose a solution to contain possible powder within the chamber and to make it accessible for cleaning.

a 60-minute vH_2O_2 gassing cycle (data not shown).

Based on the pre-study "lyo cake," lyophilized cakes of formulations FB1, FB2, and FB3 were removed and the weight of the lyophilized cake dust layer remains was determined. The FB1 lyophilized cake could be removed very efficiently, resulting in a very thin lyophilized cake dust layer and small lyophilized cake crumbles (see Figures 2C and 2D). For FB2 (see Figures 2E and 2F) and FB3 (see Figures 2H and 2G), removing the lyophilized cake was more difficult, leaving behind a thicker dust layer with larger lyophilized cake crumbles. The medium amount of removed material was 90% for FB1, 31% for FB2, and 20% for FB3.

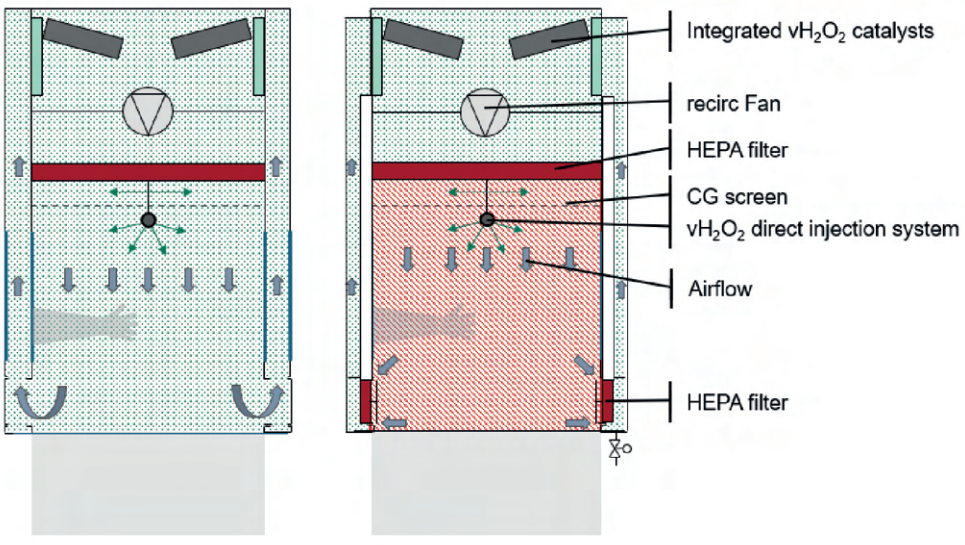
The vials with the different lyophilized cake dust layers underwent the same vH_2O_2 gassing cycle as before. After a 60-minute vH_2O_2 gassing cycle, the heat-dried formulations (data not shown) and the intact lyophilized cakes exhibited an unreduced bacterial growth rate compared to the positive control. Also, the bacterial growth rate of the FB2 and FB3 lyophilized cake dust layers were almost unaffected and the bacterial growth rate of the FB1 lyophilized cake dust layer was only marginally reduced, even after a 60-minute vH_2O_2 exposure time (see Figure 2I.)

DISCUSSION

The use of vH_2O_2 is a well-established, safe, and cost-effective method for room and full-system decontamination of visually clean surfaces after the handling of biohazardous products (postproduction cycle). This helps protect the operator, prevent the release of biohazardous products in the environment, and reduce the risk for cross-contamination within a production facility/filling line. Using vH_2O_2 as a postproduction decontamination method has advantages over formaldehyde. This is because vH_2O_2 can be removed from the system with catalysts where it is degraded to oxygen and water, leaving no liquid waste or cancerogenic substance for disposal.

Because the vH_2O_2 bio-decontamination is exclusively approved for the disinfection of visually clean surfaces, this work addressed the question of whether vH_2O_2 might be a suitable disinfectant to decontaminate surfaces contaminated with lyophilized hazardous biologicals or ATMPs. In addition, the impact of the matrix as well as the size of the lyophilized cake

Figure 3: Proposed isolator designs for (3A) filling of liquid hazardous biologicals and ATMPs with bio-decontamination of return air ducts and plenum areas and for (3B) filling of lyophilized hazardous biologicals and ATMPs.



Red = containment area; green dots = vH_2O_2

crumbles on the vH_2O_2 efficacy was investigated by using *Geobacillus stearothermophilus* as a surrogate.

The experiments demonstrated that each tested pharmaceutical relevant matrix as well as the thickness and grain size of the lyophilized BI residues have a huge impact on the vH_2O_2 decontamination efficacy (see Figure 1I). The intact lyophilized cakes of formulation FB1, FB2, and FB3 prevented the vH_2O_2 inactivation of the lyophilized *Geobacillus stearothermophilus* within the tested exposure time of 60 minutes. This might be due to a combination of following effects:

- Limited penetration capability: vH_2O_2 is known to have a limited penetration capability, therefore the German competent authority among others approves vH_2O_2 explicitly for the surface disinfection of visually clean surfaces [7].
- Dissolution of the lyophilized cake: pre-study "lyo cake" (see Figures 2A and 2B) showed that the cake dissolves during the vH_2O_2 gassing process in liquid vH_2O_2, condensed water, or probably a mixture of liquid vH_2O_2 and condensed water. Therefore, the spores are exposed to liquid vH_2O_2 instead of vH_2O_2. Research has demonstrated that vH_2O_2 in its vaporized form is a stronger oxidizing agent than in its liquid form [4]. In addition, the concentration of vH_2O_2 in the gas phase is higher than in the liquid phase [13].

Notably, the bacteria embedded in the lyophilized cake dust layers, after removal of the lyophilized cake itself, could not be inactivated, even after 60-minute vH_2O_2 exposure time, because the bacterial growth rates in FB2 and FB3 were nearly unaffected and was only marginal reduced in FB1.

In order to classify the results of the experiments correctly, it should be noted that the well-established bioindicator organism *Geobacillus stearothermophilus* presents a great challenge in the realm of deactivation. It is expected that inactivation times for hazardous biologicals and ATMPs will be extended in a similar proportion or to a similar extent depending on the formulation.

The experiments demonstrate that bacteria embedded in a dried matrix are inaccessible for the vH_2O_2 penetration, even when it is only a thin lyophilized cake dust layer or small lyophilized cake crumble. Further, the results point toward that the formulation composition (and with it the cake structure and morphology) play only a minor role in counteracting the vH_2O_2 decontamination as FB1, FB2, and FB3, which represent pharmaceutically relevant matrices, all posed a similar challenge to successful decontamination (see Figure 2I). When these findings are traced back to the actual fill/finish process, it can be concluded that lyophilized material must be prevented from accumulating anywhere in the system if vH_2O_2 is used for postproduction bio-decontamination.

To meet the challenge posed by accumulated lyophilized products inside the isolator chamber, a specialized isolator design is proposed (see Figure 3). This design aims to make the space where lyophilized product is contained clear and accessible. Especially, an accumulation in poorly accessible return air ducts or plenum areas should be prevented. Therefore, the incorporation of return

air filters, which are located directly on the isolator chamber, is suggested.

These filters capture product powder that may occur inside the isolator chamber and prevent the agglomeration of freeze-dried biohazards within the isolator return air ducts and plenum. Automatic return air filters are preventing biohazardous powder entering return air ducts and plenum areas. Filters can be changed without exposure (safe change).

The air lock filters are decontaminated during gassing with vH_2O_2, as the vapor can penetrate through the filter (data not shown). When exchanging the filters, safe change principles are applied, thus larger lyophilized cake crumbles that are not inactivated by vH_2O_2 do not pose a risk to the operator or the environment. Furthermore, the isolator design is prepared for wash-in-place integration. If based on the product, this method is chosen for decontamination after spillage of lyophilized drug product.

CONCLUSION

We found that vH_2O_2 is an effective method with wide spectrum activity for controlling contamination with biohazards. When lyophilized hazardous biologicals and ATMPs are present in the system, accumulation of the lyophilized powder poses a risk to vH_2O_2 postproduction decontamination. Therefore, during the design of the barrier system, process and safety requirements should be considered. Integrated return air filters located directly at the main isolator chamber pose a solution to contain possible powder within the chamber and to make it accessible for cleaning. The combination of postproduction decontamination and return air filter creates a robust contamination control solution for production of lyophilized hazardous biologics and ATMPs.

Acknowledgments

Ann-Catherine Roth, Katharina Westerhoff, and Dennis Kreft for execution of experiments at Franz Ziel GmbH
Holger Kranenburg, PhD, for pre-studies at Franz Ziel GmbH
Mónica Rosa, PhD, and Brecht Vanbillemont, PhD, for discussions about lyophilization matrices at Coriolis Pharma Research GmbH

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LESSONS FROM A COST OF GOODS ANALYSIS WORKSHOP

By Erich H. Bozenhardt, PE, Jeff Odum, and David Raab

Advanced therapy medicinal products (ATMPs) are transformative therapeutics that are realizing increasing gains in market approvals, yet are expensive products to produce. To enable a broader application of these medicinal products in the marketplace, the cost of goods (COGs) sold should be addressed early in development with a focus on reduction of cost to the patient.

Every drug product and the manufacturing process licensed to produce that product will have to address the COGs at some point—this is an inevitable fact. To enable broad application of medicines such as ATMPs, the COGs quite often need to be reduced for accessibility by the broader global patient population.

The design of a manufacturing process for any biopharmaceutical product involves a proven methodology that includes criteria such as operating costs, capital investment costs, and manufacturing reliability and efficiency. Success is often driven not by product-specific attributes, but by a wide range of facility attributes that can often be overlooked or given less emphasis.

2024 ISPE ANNUAL MEETING WORKSHOP

This article is the first of a three-part series focused on defining how industry views the analysis of COGs. These articles are the result of the findings from a workshop held at the ISPE Annual Meeting & Expo in October 2024. The three articles will introduce goals and objectives of the workshop, the tools that industry uses that have significant impact of COGs related to process and facility design attributes, and the methodology that was used to produce results from three different case study examples.

The focus of the workshop was to identify key factors that could be both verifiable and easily measured for short- and long-term impact, and also to identify any variables that should be addressed to validate the conclusions that were reached. To do this requires a defined methodology that addresses criteria such as operational costs, manufacturing efficiency, capital investment, and operational risk. The key is to define a tool that will provide the necessary data to evaluate the effort and present the results in a manner that is user-friendly and accurate.

Participants were asked a key question: "Where would you think the greatest impact to reducing cost of goods would come from?" The answer would be impacted by several attributes, including the manufacturing process, where the participant was assigned within their organization, the participant's experience, and the scale of the manufacturing platform.

BACKGROUND

"The cost of any form of biologic product is weighed against its therapeutic benefit in its cost–benefit analysis. This assessment includes considering the relative costs of manufacturing. The affordability of many ATMPs such as cell therapy products (CTPs) is often driven by factors related to development, clinical manufacturing logistics, and facility optimization. Because many CTP processes are not yet considered robust due to their lack of manufacturing support data, the question around COGs sometimes is not given its appropriate emphasis during early-phase design activities" [1].

A 2017 landmark study performed by the International Society for Cell & Gene Therapy accurately stated that many CTPs are developed and launched without consideration of incorporating the COGs during process development and the resulting influence of design decisions for advancing the clinical-scale manufacturing to a more commercially viable process [2]. It is critical to align early-stage process development to long-term production as soon as possible in clinical development.

The design decisions made during the conceptual design of a manufacturing asset for CTPs have consequential impacts on facility capital costs and on COGs. During clinical trials, there is tremendous focus on trial costs as companies reach their phase 3 trials, which can drive reduction of investment in facilities, equipment, and development. Decisions made years before in facility design will impact these per-patient values more than many might think. Once a process has been used to manufacture

clinical material, comparability studies will be needed for changes. These one-time costs frequently do not get funded because they can have a long return on investment and/or will delay commercial approval (i.e., lost opportunity cost).

Costs for raw materials, reagents, starting materials, labor, utilities, and consumables will be driven by market conditions. Very little impact can be influenced to reduce or improve market reality. But the facility attributes that impact day-to-day operational costs and manufacturing efficiency, once established, will become baseline. Speed to market, flexibility and efficiency, and regulatory qualification and compliance are affected as the decisions impacting COGs are baselined.

Implementing COGs analysis during early-phase facility planning brings value by shedding light on areas of operational cost risk, future per-patient trial costs impacted by facility attributes, and identification of options for consideration in equipment selection and facility design. By looking at COGs distribution for each clinical phase, it can easily be seen where facility design decisions have the greatest impact. The cost impacts—from personnel, materials and supplies, equipment, and facility attributes—significantly affect overall operational costs. The early-phase facility design decisions will therefore have a significant impact on COGs.

TOOLS

The tools required to evaluate different production scenarios are dependent on accurate data and valid assumptions that address the necessary cost model attributes. The key to success in COGs analysis is the strength of the input data. Avoiding the "garbage in, garbage out" result of improper or irrelevant data analysis is often easier said than done. Accurate data includes:

- Personnel levels
- Actual equipment costs or bid pricing, by product or case
- Energy costs based on monthly price per kilowatt-hour (kWh) billing
- Unit operation analysis of mass-balance throughput
- Consumable costs
- Facility design and construction attributes
- Environmental monitoring (EM) and manufacturing sampling frequency and costs
- Material volumes and unit costs

FACTORS

"Developing COGs values that are specifically driven by the attributes of the process/facility relationship will focus on a set of inputs and outputs that have a direct day-to-day impact on operational costs and manufacturing efficiency" [2].

Prior to selecting or developing a COGs model, several factors must be considered. Although the general purpose of the model may be to determine COGs for one or more manufacturing scenarios, the model may look very different depending on the manufacturing process, level of detail of available cost information, and cost types to be included in the COGs.

The workshop considered only cellular products; however, a similar methodology for determining COGs could also be applied to other products such as viral vectors, monoclonal antibodies, or even small molecules. The applicability of different cost categories will depend on the manufacturing process. For example, for the manufacturing processes in the workshop, purified water and process gases were purchased in containers rather than being generated on-site. For other processes that may make significant use of stainless steel vessels and require larger quantities of water for cleaning, on-site generation may be required. The COGs model would also need to account for costs associated with the generation.

Information—such as required equipment and consumable quantities as well as the number of full-time employees needed based on patients-per-year amounts—was provided to the workshop participants. These quantities were established based on design details for actual manufacturing facility projects where production modeling was completed as part of the project work. Having this information prepared for workshop participants allowed for the COGs model to function as an accounting tool to be used for sensitivity analysis and scenario comparison. More complex COGs models developed earlier in a project may include both production modeling and cost sensitivity components.

Cost of Goods Model

The simple COGs model developed for the workshop was loosely based on an Excel model developed for assessing the cost of viral vector production in an academic environment [3]. Unlike the reference academic COGs tool, the tool used for the workshop included costs and factors not considered in the academic study. These factors included energy costs for cleanroom heating, ventilation, and air conditioning (HVAC); EM costs; and facility cost depreciation.

Workshop participants were provided with the information needed for inputs to the COGs tool to assess differences in COGs associated with scale up of a cell therapy product from either an early clinical to late clinical stage or from a late clinical stage to a commercial stage. The COGs model was broken out by cost in four main areas: personnel, facility, direct materials, and equipment.

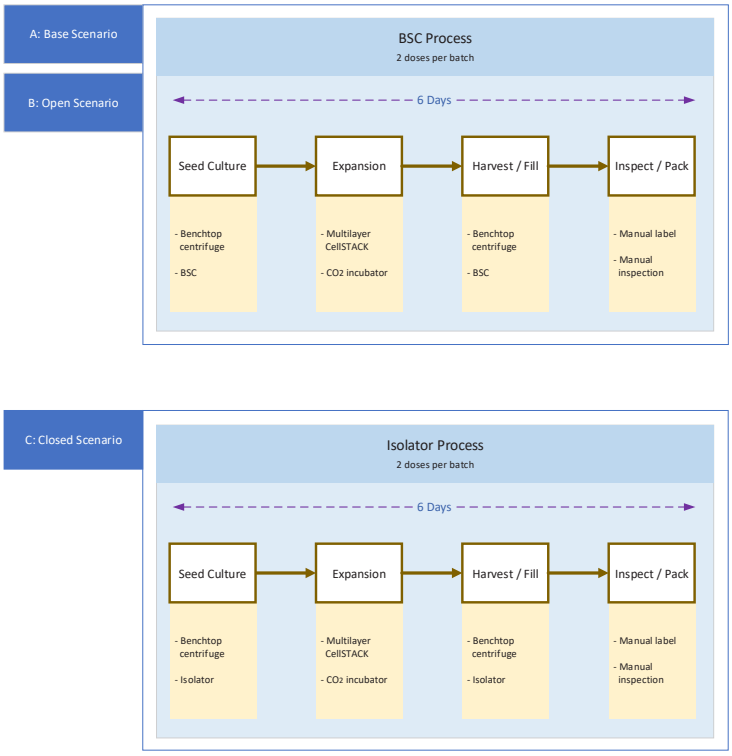
Personnel

Occupancy of a single product is based on the target production per year. The personnel category included manufacturing, nonmanufacturing, and compliance personnel. The manufacturing personnel included both supervisors and operators for various production areas. The nonmanufacturing personnel category included human resources, information technology, maintenance, warehousing, and other support personnel. Compliance personnel included quality assurance, quality control, and validation. A fixed annual salary with benefits was assumed for each employee type.

Facility

The facility category included costs associated with HVAC and EM, with assumed operating costs per square foot based on the room

Figure 1: Case 1 BFDs.



classification. Total installed cost (TIC) for the facility building was depreciated as part of the facility cost. Maintenance and taxes were included as a percentage of the building TIC.

Direct materials

The direct materials category included process consumables, raw materials, packaging and labeling materials, cleaning supplies, and product shipping costs. The direct materials costs were assumed to scale directly with the number of patients per year within the given operating scenario (development stage and process closure type).

Equipment

The equipment list is based on targeted occupancy for each case. The equipment category captured depreciation costs for process and laboratory equipment. The COGs model also included input fields for annual service costs based on equipment type, but this input was not used in the workshop.

CASE STUDIES

Three cases were based on actual facilities where operating companies are planning their next stage of manufacturing. The companies in cases 1 and 2 had very similar cellular products but were very different in terms of capital available and manufacturing goals. The company in case 3 had a very complex process but had similar capital and goals as the company from the first case. For all cases, the dosing was assumed to be a one-time treatment with one dose. The equipment requirements for each case support that dosing strategy.

Workshop participants were assigned to teams of four or more people to analyze one of the three case studies. Each team was randomly assigned a case study. For each of the case studies, three scenarios were presented for consideration: base, open, and closed. Each team was given COGs information for all three scenarios associated with their case study. The information included block flow diagrams (BFDs), manufacturing area layout drawings, equipment information, staffing information, and bill of materials. The teams were also given a copy of the COGs tool prepopulated with the relevant inputs for the base scenario for their case study.

Base Scenario

The base scenario is the starting point representing a clinical development stage. It involves open operations in a biosafety cabinet (BSC).

Open Scenario

The open scenario assumes a later clinical development stage or an early commercial stage where the number of patients to be treated increases by one or more orders of magnitude over the base scenario. It uses the same open process as the base scenario, but requires additional equipment, staffing, cleanroom space, etc., to accommodate an increased patient population.

Closed Scenario

The closed scenario assumes a later clinical development stage or an early commercial stage where the number of patients to be treated increases by one or more orders of magnitude over the base scenario. The number of patients treated in the closed scenario is the same as in the open scenario. Unlike the other scenarios, the closed scenario requires a modified process to allow for closed processing. Process closure is achieved through a combination of single-use systems (SUS) and isolators.

Case 1

Case 1 represents a young start-up corporate enterprise that is producing an allogeneic cell therapy product for early-stage phase 1 clinical trials. Like many start-ups, the company has limited resources in terms of financial capital, human resources, and knowledge of manufacturing operations, outside of their engagement with contracting development and manufacturing organizations (CDMOs) in the past.

Their investigative new drug has been approved for a clinical trial of 60 patients. Their process has a six-day manufacturing cycle, with a restocking of the working cell bank material after each 100 patients. The process yields two patients/batches, with a dosing requirement of one dose/patient. The current process is classified as open, implementing open BSCs as an environmental contamination risk mitigation strategy.

The BSC represents a higher-risk scenario for manufacturing unit operations compared with a closed system. The current clinical needs are moving production to supply 1,000 patients. The process for this product is a straightforward adherent cell expansion on a 2D surface, as outlined in the BFDs shown in Figure 1. The move from open to closed systems requires minimal process development mainly around consumables and working within the isolator.

In the case 1 base scenario, limited production for phase 1 trials, the facility uses a Grade B (ISO 7 in operation) room as the background for the BSCs and lab instruments. The base scenario layout is shown in Figure 2. The open scenario adds an adjunct processing room about twice the size of the original Grade B processing space. The closed/isolated scenario adds similar room area, but both processing rooms are Grade C (ISO 8) space.

Case 2

Case 2 involves the production of an allogeneic cell therapy therapeutic by an established biopharmaceutical company. The production focus is late-stage phase 3 clinical production for a base case of 300 patients. The process provided indicates a six-day manufacturing cycle, with a restocking of the working cell bank material after every 50 production batches. The process yields two patients/batches, with a dosing requirement of one dose per patient.

In moving to commercial production, the patient population will be expanded to supply 4,000 patients/year. Expanding to commercial production may be accomplished either in the existing open process or by moving into a larger-scale bioreactor closed-system process. The bioreactor process will yield 500 patients/batches with a dosing requirement of one dose per patient. The bioreactor process will use the

Figure 2: Case 1 base scenario layout.

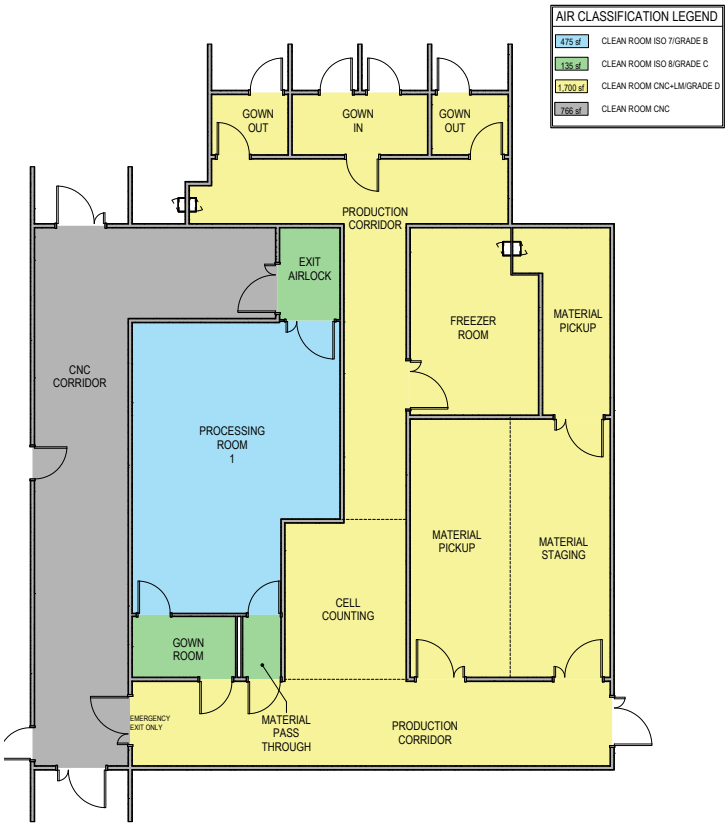


Figure 3: Case 2 BFDs.

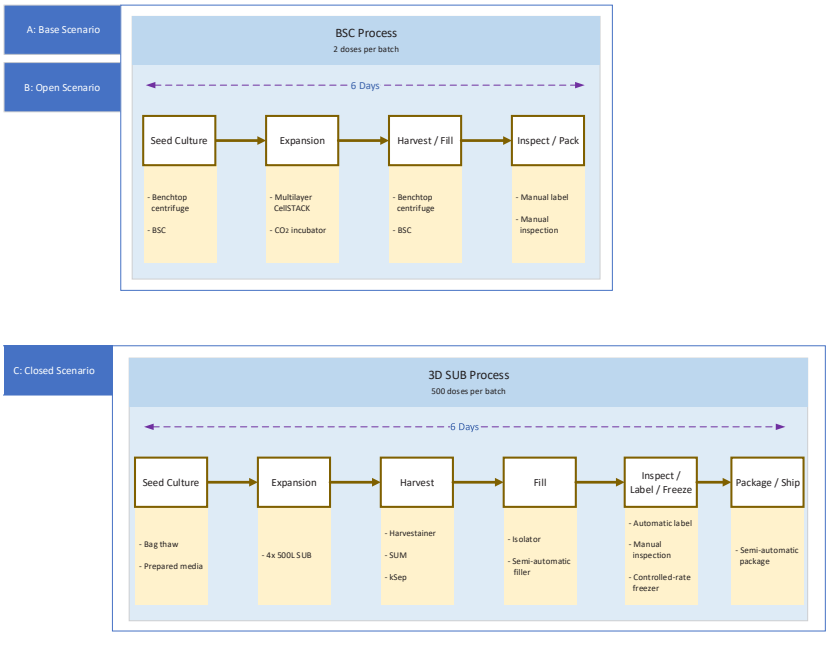


Figure 4: Case 2 bioreactor (closed) scenario layout.

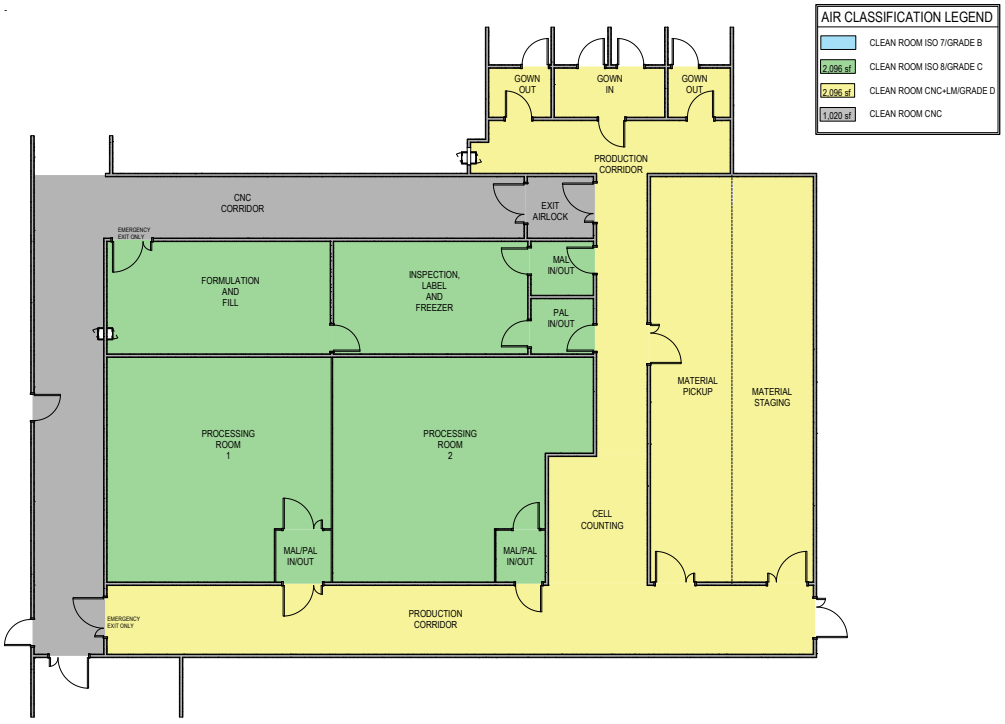


Figure 5: Case 3 BFDs.

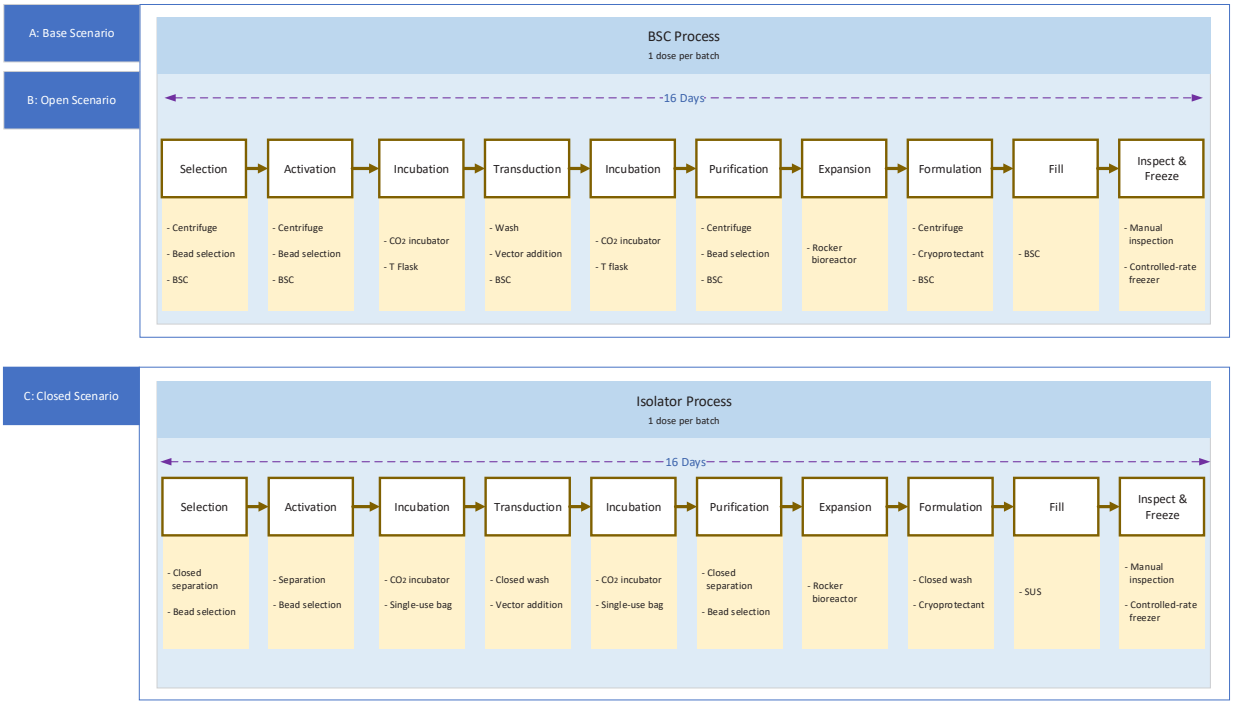


Figure 6: Case 3 base scenario layout.

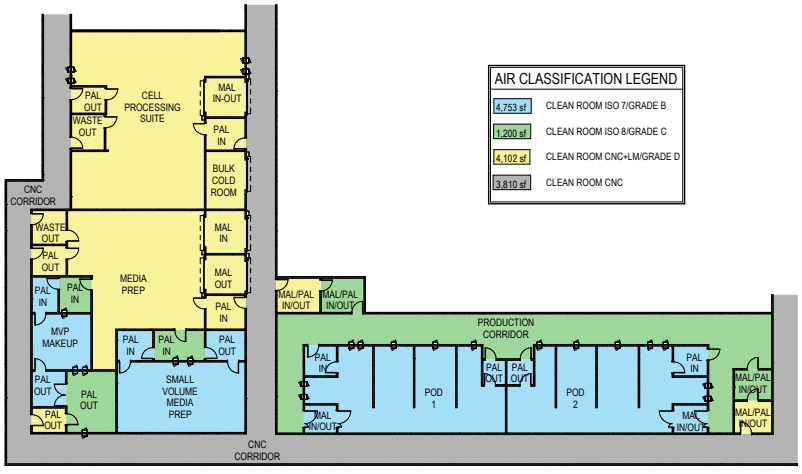


Figure 7: Case 3 closed scenario layout.

same cells as the 2D culture process, but will require significant process changes. The third part of the article series will cover the discussion on the risks and costs of using this approach. The BFDs for case 2 scenarios are shown in Figures 3 and 4.

Case 3

Case 3 is an chimeric antigen receptor T (CAR T) cell product being manufactured for early-stage phase 1 clinical trials by an early-stage development organization that has had successful market capitalization funding via venture capital organizations investment interest.

The phase 1 trial targeted a patient population of 54 individuals via an open manufacturing process. The target production increase must move to 2,000 patients per year. This can be achieved by implementation of expansion using BSCs or through closed processing into a single-use platform. The overall process duration is 16 days to produce the product. The BFDs for case 3 scenarios in Figure 5 show the same process steps between the open and closed process; however, most steps use different equipment. Significant process development will be needed to switch from an open to closed system.

The complex process and autologous nature of this product creates a different set of layouts for case 3. The base scenario layout shown in Figure 6 shows multiple small processing cores with a centralized area for common preparations. The expanded scale open process uses the same centralized area and adds small processing rooms.

The transition from an open process to closed SUS will require some process development. In this scenario, the BioPhorum closure analysis provides a realistic expectation of that development [4].

Table 1: Support areas.

	Base Scenario (ft2)			Open Manufacturing Scenario (ft2)			Closed Manufacturing Scenario (ft2)		
Case	Lab Space	Non-Lab Space	Total CNC Space	Lab Space	Non-Lab Space	Total CNC Space	Lab Space	Non-Lab Space	Total CNC Space
1	700	1,300	2,000	1,200	5,600	6,800	1,200	5,200	6,400
2	1,200	2,900	4,100	2,200	23,600	25,800	800	9,500	10,300
3	200	1,600	1,800	500	18,800	19,300	500	19,600	20,100

The BioPhorum analysis and actual commercial processes have not been able to determine a viable option for a fully closed process primarily due to starting materials. That development leads to a restructured layout that reduces but does not eliminate Grade B space to support formulations in Grade A (ISO 5), as shown in Figure 7.

To support the manufacturing operations, there is assumed to be a nonmanufacturing controlled not classified (CNC) support area for each layout. The support areas include labs as well as other spaces needed for employees and materials (e.g., offices, breakrooms, storage spaces, mechanical spaces) The breakdown of this space is shown in Table 1.

These cases are typical of the current industry mindset. Several people in the workshop recounted that they took part in a similar case evaluation or that they were from a company currently undergoing this evaluation to determine their path forward.

WORKSHOP OBJECTIVE

A closed system can impact multiple elements of facility design, including gowning, airlock design, layout and adjacencies, material, personnel and waste flows, manufacturing area classifications, HVAC, and critical utilities. The *ISPE Baseline® Guide Vol 6: Biopharmaceutical Manufacturing Facilities (Third Edition)*, established how process and facility attributes can be aligned in a manner to reduce risk to patients by implementing closed-system designs [5].

This workshop introduced attendees to the impacts of open vs. closed processing for cell therapy manufacturing. It featured case studies on operations in open vs. closed systems and the subsequent impact to layout, operational approach, and utility infrastructure, and how those impacted COGs. In the next article, we will discuss the key drivers for COGs optimization and how the tools identified in the session were implemented to produce the results from the workshop.

CONCLUSION

With the proper tools in hand, the methodology of determining COGs will be driven by the cost components previously discussed and the key performance indicators identified as critical to success. But what defines success?

The next article in this series will define the COGs analysis execution approach, the data that is required, how decision-making is performed, and the criteria that define success—cost efficiency, operational improvements, reduced waste, and inefficiency. Using the results from this workshop as a baseline, scenarios for cost reductions, facility modifications, utility optimization, and improved operations will be analyzed.

Acknowledgements

The authors would like to acknowledge the following workshop participants who will be contributors to the upcoming articles in the series: Evan Lamb, Ken Rondo, and Ryan Mazur.

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CONTINUOUS VIRAL VECTOR MANUFACTURING

By Robert Dream, PhD, and Jeff Odum

A growing segment of the advanced therapy medicinal product (ATMP) landscape, which includes gene therapies and cell-based treatments, relies heavily on viral vectors for efficient gene delivery. The increasing demand for these therapies requires a robust, scalable, and cost-effective manufacturing solution.

Traditional fed-batch viral vector production poses challenges such as variability, long processing times, and limited scalability, making it difficult to meet commercial and clinical demands. Continuous biomanufacturing (CBM) offers a potentially transformative approach by enabling consistent product quality, reducing processing time, and improving overall efficiency.

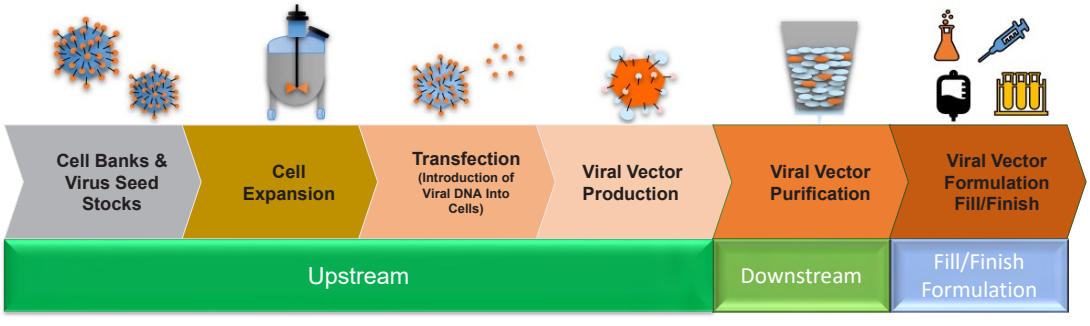
Implementing CBM for viral vector production requires careful integration of key unit operations, including viral inactivation, purification, and formulation, while ensuring regulatory compliance and process robustness. By leveraging continuous processing strategies, manufacturers can enhance the scalability, reproducibility, and accessibility of ATMPs, ultimately accelerating their path to patients.

BACKGROUND

There is a rising demand for high-quality viral vectors due to their promising therapeutic applications. In the field of vaccination, novel vaccines are being developed to address new pathogen outbreaks, and rapid and more efficient processes are required to respond as fast as possible to this demand. Viral vector–driven gene therapies have been proven efficient and safe in numerous clinical trials, and some viral vectors are already approved for commercialization. However, viral vector production is still a challenge on the pathway to clinics. Batch and fed-batch culture modes are preferred in the biologicals manufacturing industry.

Continuous manufacturing has been proven to improve viral titers and reduce the bioprocessing time and costs. In the context of viral vector production, CBM offers a number of promising advantages in terms of efficiency, scalability, and cost-effectiveness compared to traditional batch processes. Figure 1 demonstrates how continuous manufacturing can be applied to viral vector production,

Figure 1: Viral vector manufacturing workflow.



its potential improvements, and the challenges associated with implementation and operation [1].

The interest in viral vector research and development has steadily increased over the years, but production processes have been given only minor attention. The development of efficient, scalable, robust, and reproducible production processes is required to meet the increasing needs of viral vectors for gene therapy programs at a reasonable cost. The most used production systems are still batch or fed batch, most often based on adherent cells (i.e., requires attachment to a substrate or surface for growth and proliferation).

There are key criteria that shape the different viral vector production systems (see Figure 2).

Batch production of viral vectors typically suffers from low titers [3]. This is because viral vector manufacturing includes the following challenges.

Scalability

Producing large amounts of high-quality vectors for commercial applications for these products typically targets smaller patient populations. Batch sizes are much smaller than for most monoclonal antibodies (mAbs) therapeutics and often require smaller manufacturing systems.

Consistency and Stability

It is a challenge to transform the upstream process of viral vector production into a fully integrated continuous manufacturing platform that ensures the vectors remain consistent and stable over time. The transfection mix generated from plasmid DNA and transfection reagents has a limited stability. Transfection reagents that yield more stable transfection mixes are required to perform transient transfection in a truly continuous operation.

Choosing the Right Production System

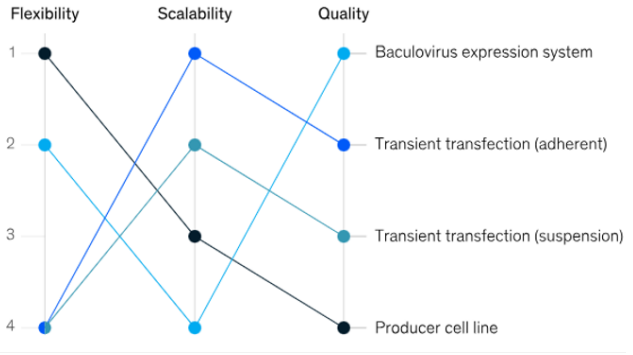
Choosing a technology platform is a crucial decision developers must make early in the process. Both adherent and suspension technologies come with their own set of advantages and challenges. Posing the right questions can help guide the evaluation and selection process:

- What is the target patient population for the disease indication? Could scalability pose a challenge during commercialization?
- Which cell lines and serotypes are planned for use?
- At what stage is process development? Is the project budget sufficient to accommodate process optimization or a potential platform change?
- What is the manufacturing strategy for both clinical and commercial stages?
- Does the regulatory filing strategy prioritize speed to market or achieving best-in-class status? Is a parallel strategy feasible, and should it be considered?

Developing Standardized Methods

Choosing the right production system, optimizing downstream processing, and developing standardized chemistry, manufacturing, and controls methods and quality assays continue to be challenges facing continuous viral vector manufacturing.

Figure 2: Key criteria that shape the different viral vector production systems [2].



MANUFACTURING BASELINE

Why would there be an interest (or need) in moving into a continuous manufacturing platform for viral vector production, especially given that it would likely pose a new set of challenges and risks for many manufacturing companies? The following sections help answer that question by looking at the key advantages.

Scalability and Improved Throughput

CBM offers a seamless, scalable process by maintaining continuous cell culture growth and viral production. This scalability allows for a more efficient transition from preclinical to clinical and commercial production without requiring the major overhauls seen in batch processes. Additionally, the ability to increase the flow rate (by avoiding the stop-clean-restart) by increasing the runtime of materials through the system increases the overall throughput, which is essential for meeting the increasing demand for gene therapies.

Scaling up viral vector production in gene therapy is traditionally constrained by the limitations of batch-based manufacturing, where each cycle requires time for preparation, execution, and cleaning between batches. This can result in inefficiencies when scaling to the larger volumes required for clinical trials or commercial use driven by market needs.

Speed to Market

In clinical settings, where time-sensitive treatments are often required, the ability to produce viral vectors more quickly can significantly reduce lead times for therapy administration during clinical trials. This ability to scale up production rapidly without compromising quality is crucial in both the clinical trial and commercialization phases. Continuous manufacturing enhances speed by eliminating production delays between batches. Because

Figures 3A and 3B: TFF systems schematic. (3A): TMP control. (3B): Permeate control with permeate pump.

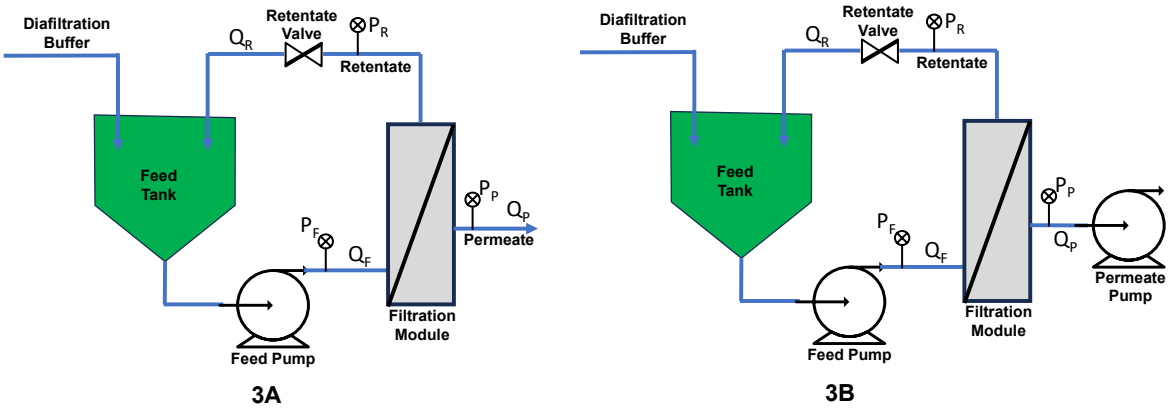


Figure glossary: Q_F: Feed Rate; Q_P: Permeate Rate; Q_R: Retentate Rate; P_F: Feed Pressure; P_P: Permeate Pressure; P_R: Retentate Pressure; TMP: Transmembrane Pressure

the process operates in an ongoing, uninterrupted flow, it enables faster production and immediate quality control.

To implement continuous manufacturing in viral vector production, some key process elements should be the focus of optimization efforts to ensure success. These key stages in the manufacturing process that benefit from continuous operations will be discussed.

Upstream Cell Culture

The upstream process for viral vector production begins with the cultivation of mammalian cells—such as human embryonic kidney (HEK) 293 cells—that are transfected with plasmids encoding the necessary genes for vector production. In continuous manufacturing, cell culture can be maintained in perfusion bioreactors, which continuously remove waste products and add fresh nutrients, allowing the cells to remain in a productive state longer than in traditional batch-based processes.

The perfusion system ensures that the cell culture environment is optimal, reducing the need for frequent harvests and enabling higher cell densities, leading to increased viral vector yields. Key critical process parameters (CPPs) such as oxygenation, pH, and temperature are tightly regulated to ensure optimal cell growth and viral production.

Downstream Purification

After viral vectors are produced in cell culture, they must be purified to remove cellular debris, unsecreted spent media components, and other impurities. Continuous downstream processing involves the use of filtration and separation technologies such as tangential flow filtration (TFF) and chromatography, which have been adapted to work in a continuous flow mode.

In TFF, the viral vectors are retained and are passed through the filtration machine to remove impurities. These systems can be scaled up with minimal changes, and their ability to continuously purify the viral product ensures consistency and efficiency throughout the production process.

Permeate-control TFF systems are commonly used in microfiltration (MF) applications where highly permeable membranes can result in excessively high flux, compromising performance and stability. For tighter ultrafiltration (UF) applications, like those requiring 30 kilodalton (kDa) membranes for antibody retention, transmembrane pressure (TMP)-control systems serve as an alternative. On the other hand, membrane cutoffs used in viral vector manufacturing, such as for adeno-associated virus (AAV), typically range from 100 to 300 kDa. These membranes offer a balance between the tighter UF membranes and the more open MF membranes, as illustrated in Figures 3A and 3B.

MANUFACTURING OPTIMIZATION

Drivers of the biomanufacturing industry are increasingly interested in the implementation of CBM because of optimization. This includes creating more with less via process intensification, reducing cost of goods for new therapeutics, providing flexibility for a changing market dynamic, and ensuring the ability to meet the growing demands of the industry for products. One attribute of continuous processes is the higher cell densities that can be achieved due to the continuous feeding of media, which often translates into higher production volume. Although the transfection that generates viral vectors differs from the traditional batch-driven protein expression, the cells must have a higher cell density to achieve the desired robust results.

There have been a number of detailed studies performed that align with the platform unit operations for viral vector manufacturing related to the production of mAb platforms [4]. Quite often, flexibility has led organizations to see that continuous manufacturing is a way to better manage complex portfolios such as viral vectors. Viral vector manufacturing is the process of creating carriers to transport therapeutic genes, which are used in

gene therapy and other fields. The process involves several steps, including the following.

Vector Design

Vectors are the vehicles used to deliver genetic material into cells. Some considerations include selecting the vector type for specific applications, designing genetic materials for specific vectors, selecting promoters for specific genes, incorporating safety features, and creating an efficient production process that includes purification and quality control testing.

Cell Culture

This step involves growing cells in a cell culture system and co-infecting them with helper plasmids. An example of cell culture in the context of co-infecting cells with helper plasmids would be the production of viral vectors for gene therapy. In this process, mammalian cells—such as HEK293 cells—are cultured in a controlled environment. These cells are then coinfected with both the viral vector plasmid (which carries the gene of interest) and a helper plasmid (which provides the necessary functions, such as proteins or enzymes) to aid in the production of the viral particles. The helper plasmid supports the replication and packaging of the viral genome, enabling the generation of functional viral vectors that can be used for gene delivery in therapeutic applications.

Purification

Purification is the process of removing unwanted materials from vectors. An example of purification in the context of viral vector production would be the use of a chromatography technique, such as affinity chromatography, to isolate the viral vectors from the culture media. After the cells have been coinfected and the viral vectors have been produced, the culture supernatant contains a mixture of viral particles, host cell debris, and other impurities. To purify the viral vectors, the supernatant is passed through a chromatography column with a resin that selectively binds to the viral particles. The bound viral vectors are then eluted, separating them from unwanted materials like proteins, DNA, and other contaminants. This process helps ensure that the final product is a pure viral vector, ready for use in applications like gene therapy.

Quality Control Testing

Quality control testing ensures the vectors are safe and pure. The implementation of CBM for large molecule viral vector drug substances requires establishing reliable analytical methods to ensure consistent product quality, safety, and efficacy. These tests should be optimized for continuous manufacturing and may require more frequent sampling or inline monitoring as the process runs continuously. The goal is to ensure robust quality control, minimal variation in product attributes, and fast detection of any process deviations.

Some of the baseline analytical tests that are commonly employed to support CBM include:

Integrity and potency assays: Functional assays, such as infectivity assays or transgene expression assays, ensure that the viral vector is intact and capable of delivering the therapeutic gene as intended. These assays often assess how well the viral vector can transduce target cells and express the desired gene product.

Purity analysis: This is an analysis of contaminants such as host cell proteins, DNA, and other impurities typically done by techniques like SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis), western blot, high-performance liquid chromatography (HPLC), or capillary electrophoresis. These ensure the viral vector is purified and free from unwanted biological material.

Endotoxin testing: This testing includes Limulus amebocyte lysate assay or recombinant Factor C (rFC) assay to determine endotoxin levels. Endotoxins can trigger immune responses, so it's important to monitor and control them during production.

Viral vector stability testing: Stability studies (e.g., accelerated stability testing) can assess how the viral vector maintains its integrity, potency, and identity under various storage conditions. This helps in understanding the shelf life of the drug substance produced via CBM.

Determination of titers: This is the quantification of viral particles—e.g., using quantitative polymerase chain reaction (qPCR), enzyme-linked immunosorbent assay (ELISA), or infectivity assays—to assess viral vector concentration. This is critical for monitoring and controlling the amount of viral vector being produced continuously.

Immunogenicity testing: This testing assesses the potential for the viral vector to induce an immune response. This could involve cell-based assays, such as T cell activation or neutralizing antibody titers, to evaluate the potential immunogenicity of the viral vector.

SELECTING THE RIGHT VIRAL VECTOR

Adenoviruses (AVs), AAVs, and lentiviruses (LVs) are three types of commonly used viral vectors for gene delivery. These recombinant viral systems have the ability to infect a broad range of hosts, including dividing and nondividing cells, without integrating with the host genome. However, there are several key distinctions between them, including packaging capacity, level, onset and duration of gene expression, and immune response.

Viral vector selection plays a crucial role in the success of continuous manufacturing processes, particularly in the production of gene therapies, vaccines, and other biologics. The choice of viral vector impacts not only the efficiency and scalability of the manufacturing process, but also the quality, safety, and functionality of the final product. The following section gives a detailed description of how viral vector selection influences continuous manufacturing.

Scalability and Yield

Continuous manufacturing relies on the ability to produce large quantities of a product in a streamlined and uninterrupted process. The viral vector used must be compatible with scalable production systems to achieve high yield without compromising quality. For instance, certain viral vectors like AAV or LV are typically used in gene therapy applications. However, their yield can be challenging to scale due to their complex genome packaging requirements or their need for specific host cell lines.

Choosing a viral vector with well-understood behavior in continuous manufacturing systems can reduce bottlenecks and increase overall productivity. For example, vectors that require fewer components for packaging (like LV) may simplify scaling, whereas more complex systems (like AAV) might need more specialized conditions or higher-efficiency production platforms.

Cell Line Compatibility

Viral vectors are typically produced in mammalian cell cultures, and the compatibility between the viral vector and the chosen cell line is vital. Continuous manufacturing systems require cell lines that can grow in large-scale bioreactors, where conditions need to be tightly controlled for high productivity and long-term cell viability. Some viral vectors may require specific helper plasmids or co-infection with additional factors to facilitate the production of viable viral particles. The more optimized the cell line and viral vector combination, the better the continuous production process will perform in terms of consistency and output.

For example, the HEK293 cell line is commonly used for LV production due to its high transfection efficiency and ability to grow in suspension cultures, which is ideal for continuous manufacturing. In contrast, AAV production often requires more complex handling and co-transfection with multiple plasmids, which could add complexity to the continuous manufacturing process.

Purification and Process Efficiency

Different viral vectors present unique challenges for purification. The choice of viral vector affects the ease and efficiency of separating the virus from host cell debris, residual plasmid DNA, and other impurities. For continuous manufacturing, a viral vector with properties that allow for easier or more efficient purification is critical. AAV, for example, requires careful filtration and chromatography steps due to its small particle size and heterogeneity, whereas LV vectors may be more readily purified through simple filtration or centrifugation methods.

The design of the purification process is critical for maintaining high product quality while minimizing processing time. In continuous systems, where viral vector production must remain consistent, purification steps must be both efficient and scalable. Poor purification can lead to contamination or loss of product, which ultimately affects the yield and safety of the final product.

Safety and Regulatory Considerations

Safety is paramount in any manufacturing process, particularly with gene therapy products that may be administered to humans. The viral vector selected must meet strict safety standards, including the absence of replication-competent virus and low levels of residual DNA or other contaminants. In continuous manufacturing, the selection of viral vectors with inherently safer profiles—such as those that are replication-deficient or have been engineered to reduce immunogenicity—helps mitigate potential risks.

For instance, when selecting adenoviral vectors for vaccine production, it's crucial to avoid wild-type AVs, which could cause adverse effects. Similarly, lentiviral vectors are typically engineered to be self-inactivating to reduce the risk of insertional mutagenesis in target cells.

Process Control and Monitoring

Continuous manufacturing requires a higher level of process control and monitoring than batch-based systems. The selected viral vector must be able to tolerate and function under conditions of continuous flow, nutrient availability, and temperature fluctuations. Additionally, real-time monitoring of CPPs such as viral titer, host cell viability, and product quality is crucial. The viral vector choice can influence the type of sensors or analytic technologies needed for process monitoring.

For example, AAV vectors often require precise control of transfection parameters, and monitoring their titers in real time can be more challenging compared to other vectors. However, recent advances in analytics and inline process monitoring equipment have made it easier to track these vectors throughout the continuous manufacturing process.

Cost and Economic Considerations

Continuous manufacturing processes aim to reduce overall production costs, and viral vector selection directly impacts the economic viability of these systems. Vectors that require fewer raw materials, simpler purification steps, or more efficient cell lines may reduce costs and increase the profitability of manufacturing. Conversely, vectors that demand complex reagents, cofactors, or multistep purification methods can lead to higher operational costs. In some cases, a viral vector with higher complexity, like AAV, might be more expensive to produce than a simpler vector, such as LV. Thus, balancing the desired therapeutic outcome with production costs is a key consideration in the choice of viral vector for continuous manufacturing systems.

AVs have a packaging capacity of roughly 8.5 kilobases (kb)—a unit of measurement used to help designate the length of DNA or RNA. One kb is equal to 1,000 bases, high levels of protein expression, and transient gene expression. The onset of expression can occur as early as 16–24 hours after infection. The high immune response from the target cells is the main limitation of adenoviral systems. Despite this, they are still widely used in research due to their highly efficient transduction of most tissue.

AAVs have a packaging capacity of roughly 4.5 kb, relatively low levels of protein expression, and the potential for long-lasting gene

expression. The tropism (the turning of all or part of an organism in a particular direction in response to an external stimulus) of AAV can also be increased via different serotypes. The primary disadvantage of AAV is its smaller packaging size for gene of interest, as well as a much later onset of expression (2–7 days for in vitro and 3–21 days for in vivo). However, this delivery system triggers very low levels of immune response.

BATCH-BASED MANUFACTURING: LESSONS LEARNED

Protein production is often less complex than viral vector manufacturing. The batch production of viral vectors primarily relies on transient transfection of human embryonic kidney HEK293 cells using multiple plasmids. However, this method often results in low viral titers. Adherent cell culture is the most common approach, but there is a growing shift toward suspension-based processes. This process typically yields lower cell densities compared to those seen in the production of recombinant proteins and monoclonal antibodies (mAbs) AAVs. Although they are more stable than LVs, they face challenges during transfection.

This step often leads to the generation of a significant proportion of "empty" or "partial" viral capsids that lack the full gene of interest. In contrast, LV vectors are more vulnerable to degradation from mechanical stress, pH fluctuations, and temperature changes, which can result in low recovery during downstream

The interest in viral vector research and development has steadily increased over the years, but production processes have been given only minor attention.

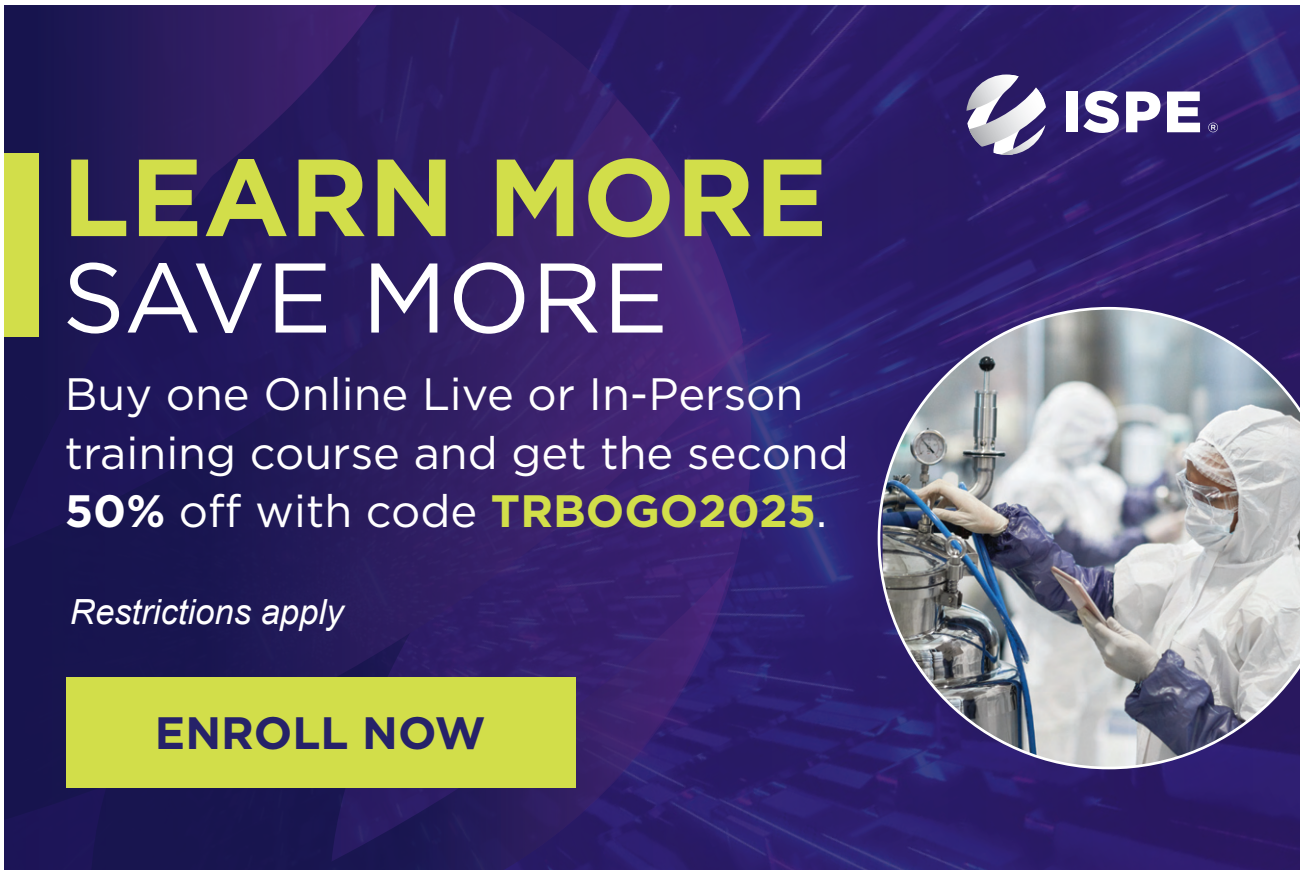
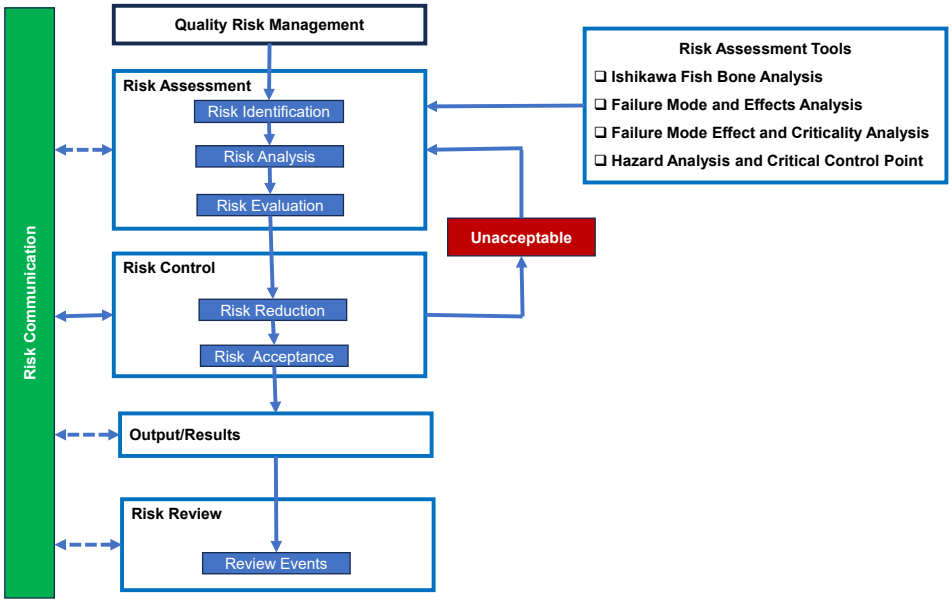


Figure 4: Initiate quality risk management (QRM) process [5].



purification. Viral vectors involve multiple proteins forming a complex three-dimensional structure that encapsulates DNA. Additionally, viral vectors tend to be more toxic to the cells used for their production than proteins.

RISK MITIGATION

In the production of certain biologic products, particularly viral vectors for gene therapy or vaccines, it is essential to operate within a biosafety level (BSL) environment. BSL guidelines are designed to protect both workers and the broader community from potential risks associated with handling biologics that may contain infectious agents or hazardous materials. This differs significantly from traditional Good Laboratory Practice systems used in mAb production, where the primary concern is generally the production of therapeutic proteins in controlled, noninfectious environments.

Hazards in Viral Vector Production vs. mAb Production

Unlike traditional mAb production—where the key hazards are often related to chemical exposure, cross-contamination, or equipment failure—viral vector production poses additional biological risks due to the inherent nature of the vectors themselves. Viral vectors, such as LVs or AAVs, may carry potential risks of unintended transmission or replication, especially in the case of replication-competent vectors. There is also a risk of unanticipated genetic modification or insertional mutagenesis when these vectors are used in gene therapy, which could potentially lead to harmful effects in recipients. Moreover, viral vectors could cause immunogenic responses or have harmful effects on the workers handling them, depending on the vector's design and the safety measures taken.

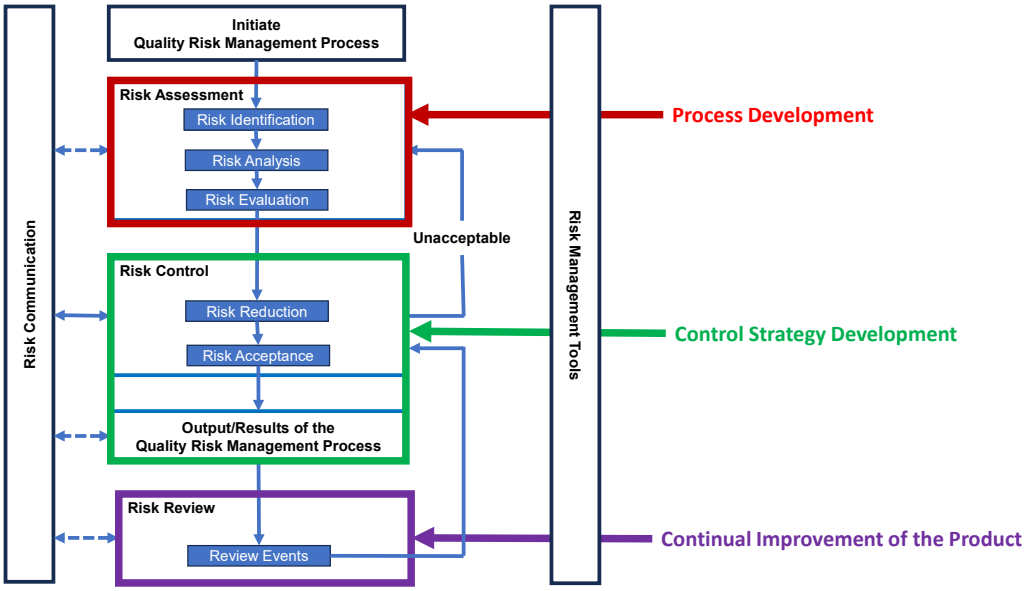
In contrast, mAb production primarily involves cultured cells—e.g., Chinese hamster ovary (CHO) cells—that produce therapeutic antibodies. Although microbial contamination is always a risk, the primary hazards are related to chemical handling—such as reagents for cell culture, purification, or formulation—and the possible risk of product contamination. As such, mAb production can typically be done within a less restrictive laboratory or production environment when compared to viral vector production, which mandates a higher level of containment to mitigate the additional biological risks.

By producing viral vectors in a BSL facility, we can mitigate these risks. This ensures that the production process is both safe and compliant with regulatory requirements. These measures are vital to ensure the safety of production workers and the public, while also guaranteeing that the therapeutic products are of the highest quality and safety.

Virus Production and Handling

Dedicated top-tier virus production and handling facilities are required to ensure the highest standards of quality and safety. These facilities are equipped with BSL-2, BSL-2+, and BSL-3

Figure 5: Overview of a typical QRM process [5].



laboratories, allowing manufacturers to manage even the most pathogenic viruses with unparalleled precision (see Figures 3 and 4 [5, 6]).

Comprehensive biosafety levels

BSL-2, BSL-2+, and BSL-3 laboratories enable the safe production and handling of a wide range of viruses, including high-potency and high-risk pathogens. This ensures that a stringent requirement of diverse applications, from gene therapy to vaccine production, is achievable.

Rigorous quality control

Maintaining the highest standards of safety and efficacy and implementing stringent quality control measures throughout the production process ensures that viral products are reliable and meet all regulatory requirements. When performing quality risk management (QRM) for the continuous manufacturing process of AAV vectors, it's crucial to evaluate several factors that could impact product quality, safety, and consistency. QRM is a structured approach to identifying, assessing, and mitigating risks throughout the manufacturing process. The following is a detailed outline of what to look for during the QRM of AAV continuous manufacturing:

- CPPs: Identify and monitor critical variables such as temperature, pH, dissolved oxygen, and glucose concentration (these can directly impact cell growth), AAV production, and viral vector quality.

> Continuous manufacturing processes aim to reduce overall production costs, and viral vector selection directly impacts the economic viability of these systems.

- Critical quality attributes (CQAs): Establish the CQAs for AAV vectors, such as viral titer, purity (e.g., absence of host cell proteins or plasmid DNA), infectivity, and integrity of the viral genome.
- Scalability and robustness: Evaluate the scalability of the process. CBM requires a stable performance at a large scale, so ensuring that process parameters remain consistent as the scale increases is essential.

A typical manufacturing run of an AAV-vector therapy using high-yield cell lines and large-capacity bioreactors might only produce approximately 10 doses of a systemic gene therapy from a single batch, at a manufacturing cost of nearly US$100,000 per dose (or, about US$4.25 million in retail).

THE RISK-BASED APPROACH

The risk-based approach is applicable to continuous viral vector manufacturing. The quality, safety, and efficacy attributes of continuous viral vector manufacture and compliance with GMP should be ensured. This should be regardless of whether viral vectors are developed in a hospital, academic, or industrial setting (see Figure 5).

Manufacturers are responsible for the quality of the viral vector they produce. The risk-based approach permits the manufacturer to design the organizational, technical, and structural measures that are put in place to comply with GMP and thus to ensure quality according to the specific risks of the product and the manufacturing process. Although the risk-based approach brings flexibility, it also implies the manufacturer is responsible for implementing control and mitigation measures necessary to address the specific risks of the product and manufacturing process.

The quality risks associated with CBM production of viral vectors are highly dependent on the biological characteristics and origin of the cells/tissues, or the biological characteristics of the vectors. This includes, for example, replication competence or reverse transcription and transgenes, the level and characteristics of the expressed protein for gene therapy products, or the properties of other noncellular components (raw materials, matrices), and the manufacturing process.

When identifying the control/mitigation measures that are most appropriate in each case, the manufacturer should consider all potential risks related to the product or the manufacturing process based on the available information. This includes an assessment of the potential implications for the quality, safety, and efficacy of the product, as well as other related risks to human health or to the environment. When new information emerges that may affect risks, an assessment should be made to determine whether the control strategy (i.e., the totality of the control and mitigation measures applied) continues to be adequate.

The evaluation of the risks and the effectiveness of the control/mitigation measures should be based on current scientific knowledge and the accumulated experience. This risk evaluation is linked to the safety of the patients.

COST IMPROVEMENTS

Many viral vector gene therapies require administering large quantities of viral particles to patients, particularly for systemic disease treatments. The large doses required for some gene therapies are challenging and expensive to manufacture [7]. A typical manufacturing run of an AAV-vector therapy using high-yield cell lines and large-capacity bioreactors might only produce approximately 10 doses of a systemic gene therapy from a single batch, at a manufacturing cost of nearly US$100,000 per dose (or, about US$4.25 million in retail). Although these costs will gradually decrease as gene therapies begin to reach clinical and commercial scales, any technological advance that reduces the required dose would bring immediate benefit, as a 10-fold reduction in dose might also bring about a 10-fold reduction in costs.

Key business case drivers for viral vector manufacturing will be the realization of reducing manufacturing costs and increasing process optimization in the manufacture of viral especially. These two drivers can be realized to an identified level, making the business case for implementing continuous manufacturing over a traditional batch-fed mAb process platform.

The four basic approaches to the decision process for moving to a continuous platform are:

- Cost-of-goods improvement: This is the most common methodology implemented.
- Net present cost (NPC): NPC is comparable to net present value (NPV) but without a revenue component. This was introduced approximately 10 years ago.
- NPV methodology using a weighted average cost of capital: In this method, you would set a product transfer price for the baseline process that gives a NPV of zero.
- Portfolio management: This is the most sophisticated analysis methodology. It considers the uncertainty across an entire portfolio of products being considered.

Many manufacturing processes are initially developed in a batch-driven mode of operations, and subsequently "transferred" to a continuous platform. There is evidence that continuous manufacturing for traditional mAbs can enhance some unit operations

in a batch-based platform. But overcoming some of the properties of the virus and the challenges around transient transfection make the move to continuous platforms more challenging.

Switching from batch-based to continuous manufacturing can lower manufacturing costs by enabling simultaneous upstream and downstream operations, reducing downtime, and increasing productivity at several-fold smaller scale. This is achieved using a range of technologies including perfusion bioreactors, single pass filtration modules, and multicolumn chromatography systems.

CONTAMINATION CONTROL AND CLOSED SYSTEMS

The majority of ATMPs and viral vector products cannot be terminally sterilized. In such cases, the manufacturing process should be conducted aseptically (i.e., under conditions that prevent microbial contamination). Manufacturing activities that may expose the product to a risk of contamination should be done in an area of appropriate environmental cleanliness level (i.e., production in a closed system, isolator, or positive pressure isolators). A background clean area of grade D is acceptable.

Isolators should be introduced only after appropriate validation. Validation should consider all critical factors of isolator technology. This includes, for example, the quality of the air inside and outside the isolator (background), disinfection regime of the isolator, the transfer process, and the isolator's integrity. Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system. The transfer of materials in and out of the isolator is one of the greatest potential sources of contamination and as such, appropriate control measures should be put in place. When materials are added or withdrawn from the closed system without an aseptic connection (e.g., use of sterile connectors or use of filters), the system can no longer be considered closed [8].

In exceptional circumstances (such as the manufacturing of the many ATMPs where viral vectors are critical to chimeric antigen receptor (CAR) T cell therapies) it is not possible to move the production to an outside cleanroom because the time between the donation of starting materials and administration of the product is very short, and the patient is also in the operating theater waiting for administration of the product. Closed systems may be placed in a controlled but nonclassified environment. Operating conditions where manufacturing activity takes place should be adequate and sufficient to ensure quality and safety of the product.

The product should not be exposed to the environment (e.g., supporting data from leak testing and pressure check of the equipment). It should be demonstrated that the clinical benefit to the patient outweighs risks linked to the absence of a classified background [4]. A detailed discussion on this topic of system closure can be found in the *ISPE Baseline Guide Vol 6: Biopharmaceutical Manufacturing Facilities (Third Edition)* [7].

CONCLUSION

The objective of moving large molecule drug substance manufacturing of viral vectors into a continuous operational platform focuses on improving manufacturing efficiency, effectiveness, and cost-of-goods improvements. These are all areas of interest for the gene therapy manufacturing companies that are looking for efficiency in improving process operations and utilization, improved control strategy, and a tool that will enhance production of key components of gene therapy products as demand for viral vector products increases.

The implementation of continuous manufacturing for viral vectors is being driven by the need for scalable, cost-effective, and efficient production to meet the increasing demand for viral vectors used in gene therapies and vaccines. Continuous manufacturing offers significant advantages in terms of productivity, process control, quality, and sustainability. It is a key enabler in advancing biopharmaceutical manufacturing for these high-demand products.

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Transforming Biopharma:
AI and Digital Transformation Center Stage at 2025 ISPE Biotechnology Conference

By Marcy Sanford

The 2025 ISPE Biotechnology Conference, scheduled for 2–3 June in Boston, MA, US, and virtually, will bring together leading pharmaceutical and biopharmaceutical manufacturers, technology providers, academic scientists, and international regulators. The meeting will offer opportunities to network, share insights, and discuss the evolving landscape and future of biotechnology product development and manufacturing.

Michelangelo Canzoneri, PhD, is the 2025 ISPE Biotechnology Conference Planning Chair. He offers advice and shares what attendees can expect at the upcoming conference.

Why attend the conference?

First, one of the themes of this conference is shaping the future of biopharma with AI, digital innovation, and regulatory excellence. Biotechnology is undergoing a profound transformation, with AI, automation, and digitalization playing an increasingly central role in drug development and manufacturing. This conference is a platform to explore how these technologies are being applied in real-world scenarios, whether in process control, regulatory compliance, or next-generation manufacturing. With expert insights from industry leaders and regulatory authorities, attendees will gain a deeper understanding of how digital business tools, AI-driven analytics, and data governance are redefining biotechnology.

Second, you'll have the opportunity to engage in critical industry discussions. We are at an inflection point where innovation must go hand in hand with compliance, operational efficiency, and sustainability. This conference brings together experts to address some of the most pressing challenges, including process intensification, facility lifecycle improvements, and supply chain resilience. Through interactive discussions, panels, and case studies, participants will gain actionable insights into the strategies shaping the next era of biotechnology.

The third reason is you'll have unparalleled networking and learning opportunities. Beyond the sessions, this conference is about connecting people. With dedicated networking opportunities, interactive discussions, and informal gatherings, attendees will have the chance to engage with regulators, industry pioneers, and technology leaders who are at the forefront of biotechnology transformation. Whether it's learning from peers or building new collaborations, these conversations will extend far beyond the conference itself.

What are you most looking forward to?

What excites me most is the opportunity to bring together a diverse group of professionals from across the biotechnology ecosystem to exchange ideas, challenge perspectives, and push the boundaries of innovation. I am particularly interested in the discussions around how, based on the *ISPE Baseline® Guide: Pharma 4.0™* approach, AI and automation are accelerating biopharmaceutical manufacturing, how regulatory expectations are evolving in a digital age, and how sustainability can be embedded into process design. These conversations will be key to ensuring that we not only innovate but do so in a way that is scalable, compliant, and impactful.

I am also looking forward to the Women in Pharma® session, which highlights the importance of fostering diverse leadership and collaboration in our industry.

Any tips for making the most of the conference?

Come with an open mind and a willingness to engage. Conferences like this are not just about listening to presentations, they are about active participation, discussion, and building relationships. Take the time to connect with colleagues, attend discussions that challenge your thinking, and explore topics that may be outside of your immediate area of expertise. Some of the most valuable takeaways often come from unexpected conversations and cross-disciplinary insights.

Biotechnology is advancing at an unprecedented pace, and the only way to stay ahead is through continuous learning and adaptation.

Why is professional development important?

Biotechnology is advancing at an unprecedented pace, and the only way to stay ahead is through continuous learning and adaptation. The emergence of AI, automation, and digital twins means that we must rethink traditional approaches to manufacturing and quality. At the same time, global regulatory landscapes are evolving, requiring us to stay informed and agile. Beyond staying current with technical advancements, professional growth is about building a network of peers and mentors who challenge us to think differently and inspire new ways of working. Conferences like this provide an essential space for that kind of learning and collaboration.

Why did you agree to be conference chair?

The biotechnology conference is not about any one individual, it is the result of a collective effort by an outstanding program committee, ISPE leadership, and industry experts who have worked together to create a meaningful, high-impact event. I accepted this role because I believe in the power of collaboration and knowledge-sharing to drive progress. The conversations happening here will shape the future of our industry, and I am honored to play a role in facilitating those discussions. Most importantly, I want to recognize the program committee for their dedication in curating an agenda that reflects the biggest opportunities and challenges in biotechnology today. Their expertise, insights, and hard work have been instrumental in making this event a success.

Any final thoughts?

This conference is about more than just presentations and panels, it is about shaping the future of biotechnology together. The challenges we face today require collective intelligence, bold thinking, and strong collaboration. A sincere thank you to the program committee, ISPE leadership, and every contributor who has made this event possible. Your efforts are what make this conference a success. I look forward to engaging discussions, fresh perspectives, and an event that will inspire all of us to continue pushing the boundaries of biotechnology.

Michelangelo Canzoneri, PhD, serves as the Global Head of Group Smart Manufacturing at Merck KGaA, based in Darmstadt, Germany. A seasoned leader in digital transformation, he acts as the key business interface across the life science, healthcare, and electronics sectors. His leadership is not only instrumental but transformative, as he fosters cross-sectoral collaboration and crafts unified strategies and roadmaps that are shaping the future of the manufacturing industry. He joined ISPE in 2016.

The 2025 ISPE Biotechnology Conference will address various themes, including the unique challenges of innovative pharmaceutical products such as biosimilars, bio betters, and follow-up biotechnology products like cell and gene therapy, advanced therapeutic medicinal products (ATMPs), and mRNA-based developments.

There will be seven tracks at the meeting:

- **Accelerating Biopharma with AI and ML: From Discovery to Delivery**
- **Analytical Enhanced Quality**
- **Biomanufacturing Facility Lifecycle: Progress, Trends, and Challenges**
- **Biotechnology Innovations**
- **Implementing Digital Initiatives in the Biopharmaceutical Industry. Where Are We on the Road Map?**
- **Operational Readiness and Cultural Excellence**
- **Process Intensification, Continuous Manufacturing, and Sustainability**

Keynote speakers include:

- **Magaly Aham, Senior Vice President Head of Global Quality Compliance and Systems at Takeda, who will share insights on how Takeda is using data, digital tools, and emerging technologies like AI to speed up product delivery, foster a culture of learning and innovation, and ensure environmental sustainability.**
- **Ronald Bauer, PhD, Head of Institute Surveillance at the Austrian Agency for Health and Food Safety (AGES), will discuss data management requirements for sterile manufacturing and share experiences with implementing Annex 1, Chapter 4, and Annex 11. He'll address how digital business tools, AI-driven analytics, and data governance are transforming biotechnology.**
- **Oliver Thiel, Vice President, Operations Commercialization, Amgen**
- **Eamonn Warren, Senior. Vice President, Global Parenteral Manufacturing, Eli Lilly and Company**
- **Timothy Watson, Vice President Head of CMC Regulatory Affairs, Gilead Sciences**

The 2025 ISPE Biotechnology Conference online
https://ispe.org/conferences/2025-biotechnology-conference

ISPE Advocates for Members with European Medicines Agency

By Kelly Schrank

ISPE is an officially recognized stakeholder of the European Medicines Agency (EMA), the agency responsible for the monitoring of medicines in the European Union. One of the ways ISPE helps its members stay at the forefront of industry challenges and changes is by interacting with regulatory authorities in the countries our members represent.

ISPE is involved in two important EMA meetings that allow our member representatives to share concerns, ask questions, and provide case studies to regulators and inspectors. These types of open exchanges allow industry to have their questions answered on innovations, evolving draft guidelines, and other topics important to the industry. Regulators appreciate interacting with industry to have open exchanges and opportunities to learn, so these types of discussions provide broad benefits to membership and the industry.

INSPECTORS WORKING GROUP (IWG) MEETINGS

ISPE is one of 16 interested parties that has been meeting with the IWG of the EMA once a year. In this meeting, ISPE and the other interested parties present their input on items of interest to their members and the industry at large, and, as a group, they ask the IWG to provide feedback on questions and concerns. ISPE has been involved since the joint industry group was formed in 2013.

In 2024, the interested parties included the following: Active Pharmaceutical Ingredients Committee, Affordable Medicines Europe, AnimalhealthEurope, Association of the European Self-Care Industry (AESGP), European Association for Logistics and Transportation in Healthcare, European Compliance Academy/European QP Association (ECA/EQPA), European Federation of Pharmaceutical Industries and Association (EFPIA), European Industrial Pharmacists Group (GPIE/EIPG), European Healthcare Distribution Association (GIRP), International Pharmaceutical Excipients Council – Europe (IPEC), International Plasma and Fractionation Association (IPFA), ISPE, Medicines for Europe, Parenteral Drug Association, Plasma Protein Therapeutics Association, and Vaccines Europe. The organizations work together under the umbrella of EFPIA to discuss topics of interest to industry and the IWG.

ISPE is honored to have the opportunity to present the voice of its members, as these meetings are open only to EMA–invited organizations. Meeting preparation starts by delivering a list of suggested topics to the EMA. The interested parties gather in meetings to determine which topics are most urgent, merge their thoughts and questions into a cohesive and concise question or concern, and draft the 20-page letter requesting to meet with the IWG.

Once a meeting has been agreed to, the EMA may ask the group to prepare short presentations highlighting their points on selected topics. The EMA may also add their own topics to the meeting, perhaps other questions, or simply feedback on items from previous meetings. Each topic has an organization designated as the leader, with the support of other organizations. ISPE often is the leader for one to two topics per meeting, as well as supporting topics that other organizations are coordinating.

For example, in 2024, ISPE led the discussion on an International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q9 EMA–IWG questionnaire. The EMA sent a questionnaire on quality risk management (QRM), and ISPE oversaw and coordinated answers from various organizations, resulting in a concise, consolidated answer delivered to the EMA at the March 2024 meeting. Specifically, the EMA provided five questions about the implementation of the new QRM Q9(R1) issued by ICH, for which the EMA was the regulatory rapporteur. Seven of the interested parties answered the questions, then ISPE provided a short presentation representing a single voice of the industry at the meeting.

Other topics at that meeting included implementation of Annex 1 (Manufacture of Sterile Medicinal Products), progress on Annex 4 (Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Medicinal Products), and Annex 5 (Manufacture of Immunological Veterinary Medicinal Products), reporting requirements related to drug shortage prevention, a potential ban of perfluoroalkyl and polyfluoroalkyl substances, and artificial intelligence (AI)/machine learning (ML) in manufacturing.

LISTEN-AND-LEARN FOCUS GROUPS

ISPE has been invited to attend the Listen-and-Learn Focus Group (LLFG) sessions organized by the Quality Innovation Group (QIG) of

the EMA. These quarterly meetings are an opportunity for industry to present case studies on innovations that are being implemented to provide the EMA with an insider view of current operations and the challenges, particularly regulatory, in manufacturing facilities.

Members of the QIG include assessors, inspectors, and other professionals from the EMA and regulatory authorities, and sometimes invited observers such as the US FDA. The meetings allow manufacturers to share knowledge and experience and to work with the QIG to identify challenges and possible solutions. By allowing industry and regulators to discuss how they assess, identify, and manage risk, everyone is learning together, which is a beneficial exchange for everyone involved.

ISPE's European Regulatory Advisor, Jean-Françoise Duliere, said of the meetings, "We consider, and the regulators consider, that we are all in the same boat and we are all learning because the technologies are quite innovative. For instance, AI, ML, platform technologies, process models, all are quite new and nobody's very familiar with them… this is why we are trying to work together."

ISPE has been involved since the initial LLFG meetings, which began only a couple of years ago. In many of the meetings, ISPE members, representing the companies where they work, have discussed case studies on the topics of the meeting. ISPE is often responsible for finding speakers on the topics of that meeting by asking relevant ISPE Communities of Practice to submit proposals on required topics.

By allowing industry and regulators to discuss how they assess, identify, and manage risk, everyone is learning together, which is a beneficial exchange for everyone involved.

The agenda for each LLFG is similar: there is an introduction to the QIG's structure and operation at the beginning followed by two sessions covering two topics, each with four to five presentations by a variety of organizations, including a plenary discussion after each one. Then, LLFGs always end with a summary of challenges, solutions, and follow-up items.

The first LLFG meeting was held in March 2023 with two sessions, each beginning with a QIG-led presentation on current regulatory requirements and discussing two case studies. The first session was on continuous manufacturing facilities. The case studies focused on 1) the continuous manufacturing of biologicals and "time-to-results" analytics challenges, and 2) enabling implementation of continuous manufacturing through process models using a vaccine platform example, presented by Merck and GSK, respectively. The second session was on decentralized manufacturing facilities. The two case studies focused on 1) autologous advanced therapy medicinal products, and 2) decentralized manufacturing individual manufacturing units, presented by Tigen Pharma and MSD, respectively.

The second LLFG meeting was held in October 2023, and the topics were digital novel technologies applied to manufacturing and quality control testing. In particular, process models and digital twins were discussed, as well as AI and ML for GMP applications. Before the first session, there was a presentation by ISPE on enabling technologies in a regulated pharmaceutical industry.

The third LLFG meeting was held in June 2024, and the topic was process models. Before the first session, there was a presentation on QIG preliminary considerations on process models by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM). A fourth meeting, held in November 2024, focused on platform technologies. The first of two meetings in 2025 was held 8–9 April and focused on personalized medicine.

The LLFGs are not open to the public, but recordings and minutes are available on the EMA website's QIG page: www.ema.europa.eu/en/committees/working-parties-other-groups/chmp-working-parties-other-groups/quality-innovation-group

For more information about ISPE regulatory operations, visit ispe.org/initiatives/regulatory

ISPE's ICH Q12 Team Trains Singapore's HSA on Regulatory Guideline

By Stuart Finnie, PhD, and Christopher J. Potter, PhD

ISPE's Q12 Implementation Team continued its series of training events with a well-attended course for Singapore's Health Sciences Authority (HSA) in November.

The team, which is part of the ISPE Product Quality Lifecyle Implementation (PQLI)® committee, has been conducting training events worldwide to assist regulatory agencies in implementing the International Council for Harmonization's (ICH) Q12 guideline, "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management."

The guideline offers a framework for biopharmaceutical and pharmaceutical manufacturers to manage post-approval changes in the chemistry, manufacturing, and controls of pharmaceutical products more predictably and efficiently across the product lifecycle. Implementing ICH's Q12 guideline is expected to promote innovation and continual improvement in production, strengthen quality assurance, and help improve the reliability of supply chain management, ultimately benefiting patients.

The training in Singapore was held virtually over four days with approximately 70 attendees. The program included sessions on key components of ICH Q12, established conditions, and Post-Approval Change Management Protocol (PACMP), also known as a Comparability Protocol in the United States. US Food and Drug Administration (FDA) representatives were on hand, providing valuable insights into the practical application of the guideline.

Implementing ICH's Q12 guideline is expected to promote innovation and continual improvement in production, strengthen quality assurance, and help improve the reliability of supply chain management, ultimately benefiting patients.

REGULATORY BACKGROUND

The guideline, which was adopted by ICH regulators in November 2019, is in the process of being implemented by ICH member

ICH Q12 has been adopted by the FDA, the Pharmaceuticals and Medical Devices Agency in Japan, the National Medical Products Administration (NMPA) in China, and the European Medicines Agency (EMA). Health Canada is in the process of integrating the guideline, as are Brazil, Mexico, Singapore, Republic of Korea, United Kingdom, Switzerland, and Chinese Taipei.

THANK YOU TO OUR CORPORATE PARTNERS

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

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regulators. To date, ICH Q12 has been adopted by the FDA, the Pharmaceuticals and Medical Devices Agency in Japan, the National Medical Products Administration (NMPA) in China, and the European Medicines Agency (EMA). Health Canada is in the process of integrating the guideline, as are Brazil, Mexico, Singapore, Republic of Korea, United Kingdom, Switzerland, and Chinese Taipei [1].

Implementing ICH's Q12 guideline is expected to promote innovation and continual improvement in the biopharmaceutical and pharmaceutical sectors, strengthen quality assurance, and help improve the reliability of supply chain management, ultimately benefiting patients. However, it has proven to be challenging. ISPE's goal is to help agencies navigate this potentially transformative guideline through training events.

THE Q12 IMPLEMENTATION TRAINING PROGRAM

PQLI® was created in 2008 to provide guidance on the practical implementation of the concepts described in ICH guidelines, focusing on Q8, Q9, Q10, Q11, Q12, Q13, and Q14.

The Q12 Implementation Team was established to collect a body of knowledge to assist the industry with the global implementation of ICH Q12. This team has delivered articles, webinars, and presentations at ISPE conferences. In addition to Singapore's HSA in 2024, it has conducted training sessions for Brazil's Agência Nacional de Vigilância Sanitária (ANVISA) in 2022, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) in 2023, and Health Canada in 2022.

The ISPE Q12 training program was created after Health Canada expressed interest in preparing reviewers for their ICH Q12 pilot program and so that reviewers would be ready to review applications with new tools/enablers under the eventual full implementation of ICH Q12 in Canada. The PQLI Q12 Implementation Team worked with representatives from Health Canada to develop the training program which addressed:

- Why ICH Q12 was required
- What the core tools and enablers are
- Using the core tools and enablers in case study examples
- An understanding of companies' pharmaceutical quality system
- An overview of the US FDA's Established Conditions pilot study experiences

The ISPE team delivered this in early 2022. The training consisted of a blend of presentations and breakout sessions. The breakout sessions had pre-prepared questions for participants to work on. Where applicable, ICH training material was used without change.

This agenda was essentially the same for subsequent training, with minor changes. For ANVISA, there was a significant emphasis on the construction and use of post-approval change management protocols (PACMPs), particularly for small molecules, since this aligned with the phased introduction of Q12 in Brazil. For the MHRA in the UK and HAS in Singapore, the agenda included a short presentation by the FDA on their experiences in implementing ICH Q12, followed by a Q&A and discussion.

SESSION 1

- An introduction to ICH Q12 and its key components
- Pharmaceutical change management system
- Breakout 1: Discussion on Q12
- Feedback and Group Discussion from Breakout 1

SESSION 2

- Introduction to established conditions with case studies examining:
  - Synthetic drug substance
  - Biological drug substance
  - Analytical procedure
- Breakout 2: Case study work on choosing Established Conditions (ECs)
  - Synthetic drug substance process
  - Large molecule drug substance process
  - Analytical procedure
- Feedback and group discussion from Breakout 2

SESSION 3

- Product Lifecycle Management (PLCM) Document (ICH material)
- Breakout 3: Presentation and case study work on developing and reviewing PLCMs based on the work done in Breakout 2.
- Feedback and group discussion from Breakout 3
- Presentations specific to agency needs or Experiences with ICH Q12 presented by another regulatory agency (e.g., US FDA)

SESSION 4

- Best practices for the preparation of a PACMP with examples covering:
  - Biological drug product
  - Synthetic drug product
- Breakout 4: Practice review of mock PACMP documents
- Feedback and group discussion from Breakout 4
- Close and any next steps

PROCESS

The training was delivered live, remotely, to reviewers and inspectors, with as many as 170 attendees split into small breakout groups. ISPE industry experts delivered most plenary presentations and were augmented by the FDA's experts in implementation of ICH Q12 who were able to add a session on their expertise in this area. Breakout group membership was pre-assigned by the agencies, as were breakout group rapporteurs. ISPE Professional Development and Regulatory Affairs staff supported the training.

FEEDBACK

Feedback on the sessions was positive, with participants liking the balance of presentations and breakout sessions and the opportunity to discuss the material presented. The attendees also liked the case studies/examples that were shared and the ability to engage with these in discussion, helping them to contextualize ICH Q12. The attendees provided some points for further improvement, which the team will use to enhance future training.

Acknowledgments

ISPE expresses deep appreciation to the PQLI Q12 Implementation working group members and their companies for their time, commitment, and access to materials:

Nina Cauchon, Amgen Inc., former ISPE International Board of Directors member

Andrew Chang, Novo Nordisk, ICH Q12 EWG representative for PhRMA

Stuart Finnie, Gilead Sciences (previously AstraZeneca)

Timothy Graul, Pfizer

Connie Langer, Pfizer

Chris Potter, ISPE Technical Projects Advisor

Saroj Ramdas, Amicus Therapeutics

Ben Stevens, GSK

Special thanks are due to Nina, Andrew, Stuart, Tim, and Ben, who delivered the training to HSA late into their evenings, including a Sunday evening, and especially to Stuart, who was online from midnight to 04:00.

In addition to preparing and delivering material for this training, members of the ISPE team were instrumental in obtaining the participation of regulators more experienced in ICH Q12 implementation to provide summaries and answer questions regarding their experiences with ICH Q12 implementation. ISPE thanks Hugo Hamel, Associate Director, Centre for Blood, Blood Products and Biotherapeutics at Health Canada, who participated in the ANVISA training, and Mahesh Ramanadham, Deputy Director, Center for Drug Evaluation and Research(CDER)/Office of Pharmaceutical Quality (OPQ)/Office of Policy for Pharmaceutical Quality and Q12 lead at the US FDA who participated in the MHRA and HSA training sessions with his team of colleagues providing their input in the late evening. The experience of these regulators provided attendees with their peers' insights into ICH Q12.

ISPE extends its gratitude to the PQLI ICH Q12 Implementation Team members and their companies for their dedication and support, as well as to the US FDA representatives and HSA liaison Dr. Subin Sankarankutty for their contributions to the training's success.

Most especially, ISPE thanks ANVISA, Health Canada, MHRA, and HSA for the opportunity to present this material and provide a forum for cross-agency dialogue, and for their valuable input to the program's design and their facilitation of the training sessions.

ISPE's PQLI Q12 Implementation Team is exploring opportunities to continue this training program with other regulatory agencies to extend the global implantation of all elements of ICH Q12.

For more information contact Regulatory@ISPE.org

Reference

1. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). "ICH Guideline Implementation." Accessed 1 April 2025. https://www.ich.org/page/ich-guideline-implementation

About the authors

Stuart Finnie, PhD, is Senior Director of CMC Regulatory Affairs for Gilead Sciences. He has many years of experience in regulatory affairs also having held positions with AstraZeneca, Amgen, and in the consulting arena. He currently serves as the Chair of the ISPE PQLI Patient Centric Specifications Team and Co-Chair of the ISPE PQLI ICH Q12 Implementation Team. He joined ISPE in 2021.

Christopher J. Potter, PhD, is a CMC Pharmaceutical Consultant. He began his career as a research scientist over 50 years ago for Beecham Research Laboratories, eventually accepting senior roles with AstraZeneca in analytical development, Research and Development Quality Assurance (R&D QA), project management, CMC documentation, and as Director of External Pharmaceutical Programs. He is a member of numerous ISPE committees and joined ISPE in 2007.

The ISPE Foundation Honors Dr. Antonio Moreira's Legacy

By Isabella Stoup

The Dr. Antonio Moreira Memorial Professional Development Fund was established in 2024 in honor of Dr. Moreira, a former Chair of the ISPE Foundation Board of Directors who passed away that same year. As a 20-year member of ISPE, he was a dedicated leader who consistently championed the ISPE Foundation and tirelessly promoted the importance of student development and engagement.

As the Vice Provost for Academic Affairs at the University of Maryland, Baltimore County, Dr. Moreira was keenly aware that in order to serve the next generation of patients, we must first provide proper training and guidance to the incoming workforce.

In the ever-changing pharmaceutical industry, the need for workforce development for up-and-coming talent is great, yet funding remains sparse. Each year, hundreds of students and recent graduates reach out to the ISPE Foundation to request financial support through the ISPE Foundation Professional Development Grants program.

Through the Dr. Antonio Moreira Memorial Professional Development Fund, the ISPE Foundation grants students and recent graduates financial support to attend an ISPE conference and receive a two-year ISPE membership. ISPE conferences provide a one-of-a-kind opportunity for young professionals to build upon their knowledge, create networks, and deepen their understanding of the pharmaceutical industry. In 2024, 37 Emerging Leaders received assistance from among 346 applications.

Individuals who have previously been awarded grants by the ISPE Foundation have gone on to sit on the ISPE International Board of Directors, joined various ISPE Conference Program Committees, and work for many leading companies within the pharmaceutical industry.

Reflecting on Dr. Moreira's deep commitment to the industry's workforce of the future, Mike Rutherford, past interim President and CEO of ISPE and the ISPE Foundation said, "Tony had a true passion for the development of students through his role in academia and through the Foundation. He supported the ISPE Foundation with great enthusiasm. He was always all in when it came to the ISPE Foundation and used every opportunity to show others the importance of supporting student development and engagement."

The ISPE Foundation invites you to reflect on the invaluable support and mentorship that have shaped your personal and professional journey by extending a helping hand to others, just as Dr. Moreira did for so many. To support students and recent graduates entering the pharmaceutical workforce, and in turn the future patients they will serve, contribute to the Dr. Antonio Moreira Memorial Professional Development Fund today by visiting www.ispefoundation.org/donate

"It is critical that we continue to support Tony's mission and passion for passing along knowledge to the next generation of students. Through the ISPE Foundation, his impact and legacy will—and must—live on," Rutherford said.

The 2024 ISPE Member of the Year

By Marcy Sanford

Niranjan S. Kulkarni, PhD, was honored with the ISPE Max Seales Yonker Member of the Year Award at the 2024 ISPE Annual Meeting & Expo in Orlando, Florida, US.

Named in honor of Max Seales Yonker, a dedicated and influential member of ISPE who served as a source of inspiration during her battle with cancer, the award honors an ISPE Member who has made the most significant contribution to the Society during the past 12 months.

Kulkarni has been active with ISPE since joining 2011, starting with his local chapter and then volunteering to help organize conferences, writing guidance documents and articles for *Pharmaceutical Engineering®*, and mentoring Emerging Leaders.

He was nominated by Sam Kitchell, Chief Operating Officer of CRB. "Niranjan has volunteered countless hours with ISPE over the years, but in the past 12 months, he seems to be especially active in nearly every aspect of ISPE," Kitchell said in his nomination letter. "It is for his exhaustive list of meaningful activities that I'm nominating him for this award. He is actively involved in multiple Community of Practice [CoP] Steering Committees and he has dedicated months of his time as a co-author on the *ISPE Guide Advanced Therapy Medicinal Products: Allogeneic Cell Therapy* and the *ISPE Guide Advanced Therapy Medicinal Products: Autologous Cell Therapy*. He's spent time preparing, presenting, and leading on-stage sessions, and still makes time to peer review articles for *Pharmaceutical Engineering*. He also encourages CRB's young professionals and his clients to get involved with ISPE and their local Chapters every chance he gets. He is an all-around champion of ISPE."

Kulkarni grew up in India, where his mother worked for Novartis. This made him aware of the importance of pharmaceutical engineering, although he did not start his career in the industry. "Initially, I worked at Dalal Engineering as a mechanical engineer working in the heavy machine industry on vibratory machines and finishing machines with centrifuges and pumps," Kulkarni said. "I came to the US for my master's degree and PhD, and learned a lot of simulation techniques, data modeling, financial modeling, and computer modeling. Luckily, I found a mentor with shared interests along the way, and he got me interested in the pharma industry again. I was curious to see how he was applying these modeling and simulation techniques in the life sciences and pharmaceutical industries."

Kulkarni has been with CRB for the past 13 years, currently serving as the Senior Director of Consulting Services. He has a doctoral degree in industrial and systems engineering from Binghamton University, Binghamton, New York, US. He is also a certified Lean Six Sigma Master Black Belt with more than 15 years of experience in business process and data modeling, operations and process simulations, process improvements, layout optimizations, and supply chain management. He has worked with the pharmaceutical, biotechnology, chemical, semiconductor, electronics assembly and packaging, and manufacturing industries.

"At CRB, we help our life science and food and beverage clients make data-driven decisions, be it justifying a business case, investing in technology, trying to improve the efficiencies of their current operations, or creating lean designs from the onset. We use modeling

and simulations, sustainability and strategic facility planning techniques, paired with Industry 4.0 (Pharma 4.0™) solutions to give clients the tools and means to make products faster without sacrificing quality," Kulkarni said.

"One of the projects I'm most proud of is one where the client asked us how they would need to expand their facility in order to expand operations," he said. "After evaluating their current processes, we determined they could accomplish their goals without moving a single wall. That was accomplished by challenging the status quo to figure out new ways of performing their tasks, improving the way they had laid out their processes and lines, and identifying resource-sharing opportunities. With that, the need for expansion was completely eliminated and they were able to get their target goals for the next five years in the space that they had."

"Another one I'm proud of is more personal. We were designing an ATMP facility that would be producing therapies to fight cancer. The technology was still not quite commercial and there were a lot of unknowns. At the time, one of my family members had cancer and I knew they could benefit from the treatment. So, I was constantly asking myself, 'How do we get this to the patient faster? How can I reduce the turnaround time, knowing that the owners don't necessarily have an infinite supply of resources to allow that to happen?' It was a nice challenge. We did a lot of simulations, a lot of modeling to figure out how the operation should run or what happens if certain things don't work the intended way, and come up with the mitigation plan. We used all the information we had to inform the design and layout."

Kulkarni says that digital innovations and computing technology have come a long way since he first started using them and that he thinks they will continue to improve and help bring about innovation in the pharmaceutical industry. "When I started simulations as a student way back, it was like moving blocks. But now, with the advancement of computing power, it is running so much more efficiently, and we can have parallel computing. The animation capabilities have really evolved so that you can visualize what's going to happen in your facility during operations or construction. With parallel computing, you are able to run simulations very, very fast to the point where it can truly be a digital twin of the facility where it's running almost near real time. And you can see what will happen if there are changes in the manufacturing process and what changes need to be made on the manufacturing floor."

Constantly learning about new processes, techniques, and technologies is at the heart of everything Kulkarni does. ISPE has helped him tremendously, he said. "I enjoy learning immensely and have received so much knowledge from ISPE. The presentations at conferences, the Chapter, and webinars are very informative and important. When you begin networking, you are amazed at the amount of knowledge, experience, and diversity within the membership. ISPE brings it all together in one place. I was very fortunate to get a lot of good mentorship and encouragement from senior management at CRB and through the ISPE Boston Chapter.

"At the Chapter level, you can evolve as a leader, you can network and really figure out how you can help the industry. I am here thanks to a lot of support that I've received and I want to pass it on. Our Emerging Leaders truly are much more curious than I was back then. They're asking good questions. They are exposed to a lot more information than we were when we were younger. I want them to have the same opportunity, or more, than I had. I try to help them understand what they can offer to the community, and at the same time, instill the philosophy of giving back to the community. I encourage them to get involved. It is very rewarding to see the amount of energy and refreshing ideas they bring to the table," Kulkarni said.

His volunteer experience is long and diverse. He serves on the ISPE ATMP and SCOPE CoP steering committees, co-authors ISPE Guidance Documents, and helps organize ISPE conferences. Kulkarni is involved with the Institute of Industrial and Systems Engineers. He also helps his parents with supporting a village in Maharashtra, India, where they provide education in math, accounting, and communications and provide financial support so villagers can buy equipment and supplies to set up small businesses.

"I feel, at the end of the day, helping people is the most important thing you can do. It doesn't matter if it is by providing medications through the work that we do or giving time—both are equally important," he said.

Meet the ISPE STAFF

XUANDAI HOANG

Hometown: Tampa, FL

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Xuandai Hoang, Senior Member Services Coordinator in the Membership Department.

When did you join the ISPE staff?
I joined the ISPE staff in December 2000 after working here as a temp. At first, I was just looking for a job while in school, but then I started to enjoy it and decided to join the customer service team.

Tell us about your role at ISPE: What do you do each day?
Each day is different but my daily tasks include answering members and customers' emails and phone calls, processing membership and event/webinar registration, and assisting other departments with their requests.

What do you love about your job?
Customer satisfaction is my number one priority. I want to make sure that our customers are happy and have positive experiences with our membership and services.

What do you like to do when you are not at work?
I love walking and gardening. I walk every day for about one hour. Right now, I am growing herbs, vegetables, and fruits in my garden. I also have two little wildflower beds for the pollinators.

ISPE ENGAGE LAUNCHES VOLUNTEER PORTAL

ISPE has launched a new feature on ISPE Engage, providing members with a portal to explore volunteer opportunities across the organization.

Volunteering can help members build new connections, strengthen their professional network, gain additional skills, and give back to the industry. Previously, opportunities were made through personal connections or general communications, but now members can search the ISPE Volunteer Program Portal for opportunities available to all members at any level. Opportunities include joining program committees, contributing to iSpeak blog posts, conducting peer reviews for ISPE guidance documents, and much more.

For more information, visit: the ISPE Volunteer Program at https://cop.ispe.org/volunteer/opportunities-list-public

VOLUNTEER PROFILE

MASSIMILIANO CESARINI

STERILE PRODUCTS PROCESSING COMMUNITY OF PRACTICE CHAIR

Massimiliano Cesarini, MEng, was named CEO of Biogenera SpA, Bologna, Italy in 2024. He began his career at Duferco Engineering in energy generation, then moved to Comecer Group, holding roles as project and product manager, and global sales manager for the pharma and advanced therapy medicinal product (ATMP) division. He eventually joined Omnia Technologies Group establishing the Omnia Life Sciences brand. He chairs the Sterile Products Processing (SPP) Community of Practice Steering Committee for ISPE, and is a member of the Knowledge Network Council. He's also Co-Chair of the team working on the good practice guide on airflow pattern visualization. He has been a member of ISPE since 2009.

Why pursue a career in the pharma industry?

From a young age, I was drawn to fields that combined innovation with a clear impact on people's lives. During my studies, I became fascinated by how science and engineering could be applied to improve healthcare outcomes. The pharmaceutical industry, with its potential to develop lifesaving technologies and medicines, felt like the perfect match for my skills and interests. This motivation has only deepened over time as I've witnessed the critical role the industry plays in global health.

What do you do in your current role?

I currently serve as the Chairman and CEO of Biogenera, an Italian biotech company that develops precision medicine technology based on peptide nucleic acids technology. Our first candidate drug is set to enter clinical trial phase 1 later this year. I lead the company's strategic vision, drive innovation in drug development, and oversee operations to ensure we are making meaningful advancements in patient care. It is an incredible privilege to be at the forefront of such transformative work.

What do you enjoy most about your work?

I enjoy most the dynamic and challenging reality of a biotech startup like Biogenera. Every day presents opportunities to solve complex problems, push the boundaries of innovation, and navigate uncharted territories in drug development. Knowing that our first drug, aimed at pediatric patients, is entering clinical trial phase 1 this year is particularly meaningful to me. The ability to contribute to treatments for children, which is a cause close to my heart, makes this work deeply fulfilling.

Tell us about a project you're proud of.

One of the most rewarding projects I've worked on was the launch of a division dedicated to ATMPs. At the time, we were at the forefront, pioneering what has now become a competitive and rapidly growing market. Leading this initiative required vision, collaboration, and adaptability, and I'm proud of how we anticipated industry trends and set the stage for innovative advancements in this field.

What do you see next for your area?

The pharmaceutical industry is moving toward increased automation, digitalization, and sustainability. For biotech startups like Biogenera, the next big advances will come from leveraging artificial intelligence to accelerate drug discovery and development and from fostering strategic partnerships to bring innovations to market faster. These advancements will play a crucial role in addressing unmet medical needs and improving patient outcomes across various therapeutic areas.

What advice would you give Emerging Leaders?

Stay curious and never stop learning. The pharmaceutical industry is constantly evolving, and Emerging Leaders need to stay ahead by understanding both the technical and regulatory landscapes. I would also emphasize the importance of collaboration and building strong professional networks. Lastly, always keep the patient at the center of what you do. This perspective will guide your decisions and inspire your work.

What do you gain from volunteering with ISPE?

My work with ISPE has been incredibly rewarding, particularly as the chair of the SPP CoP. It's a privilege to collaborate with such talented professionals and contribute to advancing knowledge in this critical area. ISPE has provided me with unparalleled opportunities for professional development and networking. What I enjoy most, though, is the sense of community and shared purpose among members.

— Marcy Sanford, ISPE Production Manager

VOLUNTEER
PROFILE

KRISHA PATEL

ATMP COMMUNITY OF PRACTICE CO-CHAIR

Krisha Patel is Co-Founder of Assurea LLC, a digital compliance consulting firm that provides IT and validation services, software assurance, and custom artificial intelligence solutions for biotech companies.

With a degree in bioprocessing science and more than 12 years of experience in computer system validation and quality assurance, Patel has worked with cell and gene therapy companies, and pharmaceutical manufacturers to ensure their systems meet regulatory standards.

In addition to being the Co-Chair for the ISPE Advanced Therapy Medicinal Products Community of Practice, she is the Co-Chair for the ISPE Carolina-South Atlantic (CASA) Chapter's education committee and helped plan the educational tracks for this year's CASA Annual Tech Show. A member of ISPE since 2019, Patel is also a member of ISPE's Women in Pharma®.

Can you describe a memorable project?

One project I'm especially excited about is Assurea's expansion into emerging tech. This year, we launched AI-powered solutions to help clients automate processes like annual product reviews, documentation review and analysis, inventory management, and shipping lane validation. It's exciting to see how our custom AI solutions will help our clients streamline operations and drive efficiency in life sciences.

As Assurea grows, we are committed to expanding our global impact in STEM (science, technology, engineering, and mathematics)—solving problems and creating waves for positive change. Our #RootingForYou campaign was created to help women and underrepresented groups get recognized for their ideas in STEM. We promote this mission through our goal-setting programs, including STEM KITS for Students, highlighting inspiring leaders, and hosting workshops with our journal prompts.

We're especially excited about the STEM KITS for Students initiative, which is designed to spark curiosity in the next generation by showing how STEM experiments connect to everyday life. It's been incredible to see this initiative grow, and we're excited to keep building on it.

What's next for your area in the industry?

I see the pharmaceutical and biotechnology industries evolving faster than ever, especially with the increased adoption of emerging technologies such as AI and blockchain. More companies are turning to AI to streamline everything from quality processes to regulatory compliance, making data analysis and decision-making more efficient and insightful. It's exciting to see how technology is no longer just a tool but a driving force in shaping the future of biotech.

The industry is recognizing the need for purpose-built process automation and advanced analytical tools to enhance the efficiency and scalability of cell and gene therapy manufacturing where this shift is especially important because scaling up manufacturing has been a challenge. The industry is realizing that off-the-shelf solutions aren't enough: we need automation and advanced analytics designed specifically for C&GT. As AI and automation become more embedded in the process, they'll help streamline development and improve efficiency, ultimately making these therapies more accessible to patients who need them.

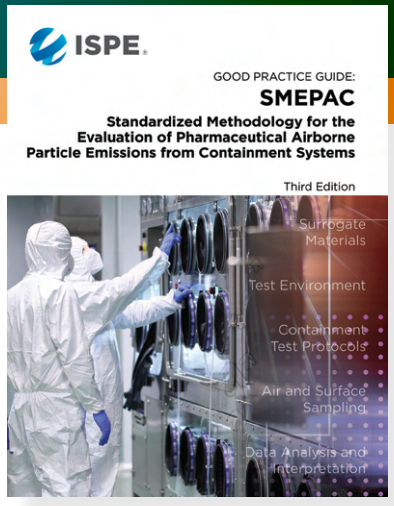
What projects is your group working on?

We have a lot of exciting initiatives coming up in the ATMP CoP. I'm especially excited about our latest initiative—a united Asia-Pacific (APAC) region ATMPs CoP collaboration which kick off at the 2025 ISPE Japan Affiliate Annual Meeting in Tokyo, Japan. Until now, ISPE affiliates in APAC regions like Singapore, Malaysia, India, Japan, South Korea, Australia, and others have had their own individual CoPs, each hosting local initiatives. For the first time, we're bringing these groups together to foster cross-collaboration across the region. Representatives from the ATMP CoPs from each APAC affiliate will now meet monthly to combine efforts and enhance engagement in the C&GT community through webinars, technical articles, and regional events. Additionally, we're in early discussions to establish an ISPE ATMP CoP for the Middle East and North Africa (MENA) region, recognizing the rapid growth of C&GT in that area of the world. Countries like Saudi Arabia and the United Arab Emirates are making major investments to position themselves as biotech hubs. For example, Saudi Arabia has established a national biotech strategy in an effort to become an international biotech hub by 2040. By engaging with these emerging markets, we hope to foster collaboration and knowledge exchange, supporting the region's expanding C&GT ecosystem.

— Marcy Sanford, ISPE Production Manager

Assessing Containment Equipment and Systems with New ISPE Guide

By Marcy Sanford



Effective containment systems in a pharmaceutical manufacturing facility are essential to protect the health of workers, the environment, and patients receiving the medications. Particles released into the facility can cause adverse side effects to facility employees, and particles released outside the facility can harm the atmosphere and nearby waterways.

ISPE originally published the I*SPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment* in 2005 to help engineering, design, and containment equipment professionals evaluate the performance of containment equipment and systems [1]. A second edition was published in 2012. Both were widely known in the industry as the "SMEPAC" Guide.

Technology and medicinal ingredients have evolved rapidly, so it was time for a new edition, and a new title. The I*SPE Good Practice Guide: SMEPAC – Standardized Methodology for the Evaluation of Pharmaceutical Airborne Particle Emissions from Containment Systems*, 3rd Edition addresses the differences between the containment performance of individual components versus a complex process. It provides updated technical guidance and standardized methodologies for evaluating the particulate containment performance (particle emissions) of pharmaceutical equipment and systems.

"The ISPE SMEPAC Guide is seen as the industry standard and has been used to assess the verify containment performance for pharmaceutical equipment and containment systems for 19 years," said Guide Co-Lead George Petroka, Principal, IES Engineers. "In addition, the experience gained performing numerous containment performance assessments (CPAs) since the second edition identified topics in the Guide that required additional explanation such as data analysis, sampling strategy, sample types, sample locations, and liquid surrogates. The third edition also addresses improvements in pharmaceutical manufacturing technologies such as continuous processing and integrated containment systems and updated containment performance protocols to assess these systems."

"The active pharmaceutical ingredients that companies produce to treat patients are becoming more and more potent, making CPAs very important," said Guide Co-lead Karen Whitaker, Associate Director, Industrial Hygiene Center of Excellence, Merck. "This Guide outlines a framework to assess containment performance and verify that it meets the agreed-upon target between the equipment vendor and the purchaser."

This Guide is intended to be used by industry professionals for the selection, containment performance, and operation of pharmaceutical equipment. "This Guide can be used to evaluate equipment both before it is purchased or anytime during its life cycle," said Guide Co-Lead Rainer Nicolai, PhD, Product Owner Engineering Consulting, F. Hoffmann-La Roche AG.

"It was researched, written, and reviewed by subject matter experts from all over the world," Nicolai said. "In addition to chapters on sampling strategy principles and analysis, interpretation, and documentation of data, it includes containment equipment test protocols for a variety of containment systems including downflow booths, unidirectional airflow booths, isolator/glove boxes, and flexible-film enclosures. It should be helpful to identify limitations of equipment or provide data that the equipment is working as intended."

For more information on this and other ISPE guides, visit ispe.org/publications/guidance-documents

Reference:

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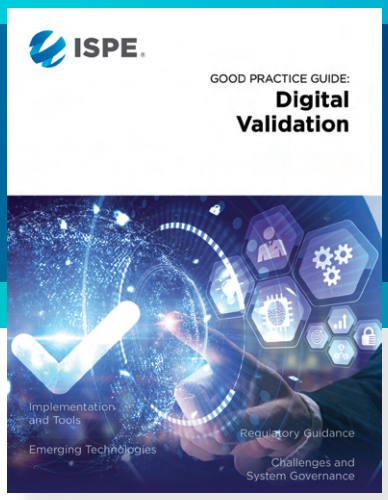
New Guide Helps Pave the Way to Digital Validation

By Marcy Sanford



The ISPE Commissioning & Qualification (C&Q) Community of Practice (CoP) conducted a survey in 2023 on the adoption of integrated C&Q, specifically on the use of paperless digital systems for planning, executing, and reporting C&Q activities. The survey revealed that 74% of respondents planned to use Digital Validation Tools (DVTs) for C&Q by 2024.

"Over the last five years, there has been a huge shift in the industry looking for more efficiency around validation and compliance. Digital Validation Tools help with quality, compliance and make processes much more efficient, with the long-term goal to mine the data and leverage it, so that an almost real time verification process is achieved," said Philip Jarvis, Validation Director, Grifols (GWWO), Co-Lead of the recently published *ISPE Good Practice Guide: Digital Validation*.

As organizations move toward digital validation of C&Q, they often face obstacles with implementation, governance, system integration, and regulatory adherence. The evolving landscape of global regulations, the variety of available technologies, and the heightened auditor expectations further complicate this transition, making structured guidance and industry-wide collaboration essential.

"The industry has had access to Digital Validation Tools for a long time, but these have finally come to realization in the last few years thanks to advances in technology. As people have started the process of moving from a paper-based to digital-based validation, there were a lot of questions about how to manage the processes, how to best leverage the tools, and many people were looking for guidance on what to do and how to do it," said Mark Drinan, Small Molecule OpU Lead, Commissioning, Qualification and Validation, Takeda, Guide Co-Lead.

The *ISPE Good Practice Guide: Digital Validation* offers practical, risk-based best practices for defining, implementing, and managing DVTs within a regulated environment. Developed by a global team of experts in validation, regulatory compliance, quality assurance, and digital transformation, this Guide presents real-world insights, case studies, and structured methodologies to facilitate the successful integration of digital validation into business operations. It explores regulatory considerations, system selection, data management strategies, and compliance frameworks, equipping organizations with the necessary tools to enhance validation efficiency while maintaining regulatory rigor.

"Both Phil, myself, and some other members of the Guide team has been through rollouts of Digital Validation tools. Successfully implementing a digital validation strategy requires more than just technology - it demands a cultural shift, cross-functional collaboration, and alignment with organizational objectives," Drinan said. "You do not just want to switch to paper on glass, you have to think digitally. In this Guide we discuss how to foster a shared understanding among quality professionals, validation experts, regulatory authorities, and technology providers, to ensure a holistic approach to digital validation. It will serve as an essential reference for organizations at all stages of their digital validation journey, whether they are beginning their transition or seeking to optimize existing systems. Even if you already have DVT in place, this Guide can help you make it better."

DVTs offer real-time visibility of progress including immediate updates on documentation status, eliminating the need for traditional manual tracking and ability to link requirements/CDEs directly to verification tests, streamlining document creation, review, report generation, and enabling faster system handovers. Additionally, they facilitate remote work, eliminate the cost and potential waste of paper-related products, eliminate the need for storage warehouses, and unify validation approaches across an organization. "We successfully set up a DVT system at AbbVie and it was very favorably received by auditors. If you are looking to drive innovation and create a more efficient process, digitizing validation is your first step," said Jarvis.

Drinan added, "This Guide can help you get to the last step of an old paper-based process and take your first step on a new journey to full digitalization."

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

QUIZ ANSWERS

Rises, Failures, and Changes in the Global ATMP Market

CONTINUED FROM PAGE 9, "GAMIFICATION"

1.The correct answer is b.
According to the US FDA, 44 cellular and gene therapy products have been approved as of March 6 in the United States [1].

2. The correct answer is all of the above.
Fidanacogene elaparvovec (Beqvez, previously Durveqtix) was approved in July 2024 by the European Commission for the treatment of severe and moderately severe hemophilia B in adults without a history of factor IX inhibitors and without detectable antibodies to variant AAV serotype Rh74 [2]. Onasemnogene abeparvovec (Zolgensma) was approved in May 2020 by the European Commission to treat spinal muscular atrophy in babies and young children with a bi-allelic mutation in the SMN1 gene [3]. Eladocagene exuparvovec-tneq suspension (Kebilidi in the US, or Upstaza in Europe, was approved by the Eurpean Commission and in Japan in July 2022 as a treatment for AADC deficiency (it was approved in the US in November 2024) [4]. Exagamglogene autotemcel (Casgevy) was approved by the European Commission in February 2024 for sickle cell disease and transfusion-dependent beta thalassemia (TDT) [5]. In the US, it was approved by the Food and Drug Administration in 2023. At the time, it was the first FDA-approved treatment to utilize a novel type of genome editing technology [6].

3. The correct answer is b.
As of 2024, the Asia-Pacific region is expected to see the fastest growth within the ATMPs market. Growth is being driven by more investments in healthcare infrastructure, rising prevalence of chronic diseases, and a growing interest in innovative therapies [7].

4. The correct answer is c.
While AstraZeneca acquired EsoBiotec in March to "advance its cell therapy ambition [8]," Roche acquired Poseida Therapeutics in January 2025 to enhance its CAR T therapy capabilities [9], and Kyowa Kirin acquired Orchard Therapeutics in January 2024 to strengthen its gene therapy pipeline [10], Pfizer continues to develop its pipeline through internal research and collaborations with no recent acquisitions.

5. The correct answer is a.
According to a HiTechHealth 2024 ATMP Review, there are 2,981 ATMP developers globally. At 1,262, North America has more developers than any other region of the world. The second most populous region is Asia-Pacific with approximately 888 developers followed by Europe with 543 developers [11].

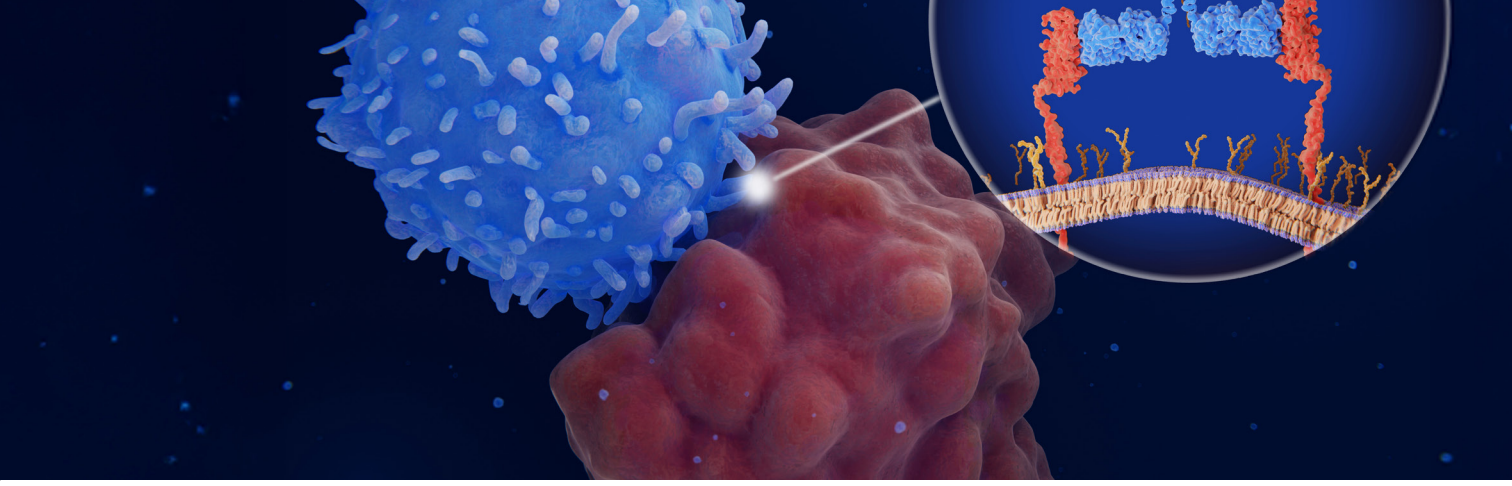
6. The correct answer is b.
The UK Medicines and Healthcare Products Regulatory Agency (MHRA) published a revised roadmap for the regulatory framework for medical devices in December 2024 [12].

7. The correct answer is d (Lifileucel).
Lifileucel (Amtagvi) has not been discontinued post-approval. It received accelerated approval from the FDA in February 2024 for the treatment of adults with unresectable or metastatic melanoma [13]. Glybera (alipogene tiparvovec) was withdrawn from the market by uniQure in 2017 due to limited usage and high costs [14]. Zalmoxis faced challenges with its phase III trial and was eventually discontinued in 2019 [15]. ChondroCelect was discontinued in 2016 after TiGenix decided not to renew its marketing authorization [16].

8. The correct answer is all of the above.
According to an October 2024 report by IQVIA, Europe continues to be a strong performer in commercial multi-country clinical trials, but it is losing global share falling from 25% in 2013 to 19% in 2023 [17].

9. The correct answer is false.
For the first time ever, the prevalence of gene therapy trials for oncology has dipped below 50%. According to a Q3 2024 report by the American Society of Gene and Cell Therapy, newly launched clinical trials are increasingly for other conditions outside of oncology. New non-oncology clinical trials rose from 39% in Q4 2023 to 51% of trials started in Q3 2023 [18].

10. Answer d is false.
While CAR T cell therapy has been growing in Sweden since it was approved in 2019 for the treatment of lymphoma and acute lymphoblastic leukemia, it is most commonly used in the United States, followed by China. The US has led the way



in research, development and approvals of applications for CAR T cell therapies [19]. Phase 1 clinical trials for Advanced Therapy Medicinal Products (ATMPs) in the UK saw a significant increase of approximately 70% from 2019 to 2024 [20]. Celgene Ltd in the US and Mesoblast Ltd in Australia are the most active ATMP developers, followed by Amgen Ltd in the United Kingdom and Ireland, Iovance Biotherapeutics Inc. and Kite Pharma in the US [21]. And, according to the NIHR Innovation Observatory of Newcastle University, 83% of ATMP clinical trials are for monotherapy while 17% of trials focus on combination therapy [21].

Rebecca Roscher, MSc, is a Project Manager at the GP Grenzach Produktions GmbH, a Bayer-owned production facility in Grenzach-Wyhlen, Germany. She is a trained scientist in molecular medicine specializing in the research and development of new drug agents/therapeutics focusing on immune therapies and cell and gene therapy platforms. As the Ex Officio member of the ISPE International Board of Directors for 2024-2025, Rebecca represents and advocates the interests of young professionals as part of the ISPE Emerging Leaders Community of Practice. She has been a member of ISPE since 2020.

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