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November/December 2023 | Volume 43, Number 6

Cell and Gene Therapy

Design Considerations for Large-Scale Stem Cell Manufacturing

Delivering Curative Therapies: Autologous vs. Allogeneic Supply Chains

Optimizing Cost of Goods for Cell Therapy Manufacturing

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Cell and Gene Therapy

14 DESIGN CONSIDERATIONS FOR LARGE-SCALE STEM CELL MANUFACTURING

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ON THE COVER The DNA and vial imagery represents the interconnectedness between genetic material and cell-and-gene-based therapeutic advancements.

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42 COMPARABILITY CONSIDERATIONS FOR CELLULAR AND GENE THERAPY PRODUCTS

Cell and gene therapy (C&GT) products comprise a rapidly growing field of innovative medicines that hold the promise to treat and, in some cases, cure diseases that are otherwise untreatable. In this article, we provide points to consider when evaluating the comparability of C&GT when changes are made in their manufacturing processes.

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Process capability is a fundamental concept for manufacturers. Pharmaceutical, biopharmaceutical, and medical device manufacturers leverage capability analysis along with other statistical quality control techniques to enable timely supply of quality medicine to patients.

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By Michael L. Rutherford


Michael L. Rutherford

Thank You and Here's to a Phenomenal Year in 2024

This is my last column in *Pharmaceutical Engineering®*. It has been my real pleasure and an honor to serve as your International Board Chair. Thank you for your support and I, like you, look forward to another phenomenal year for ISPE in 2024.

We had an awesome 2023 ISPE Annual Meeting & Expo in Las Vegas, Nevada. It was great seeing so many of you there, including our second group of 2023 ISPE Student/Recent Graduate Grant recipients. Just like all of you, these students and recent graduates had the opportunity to attend numerous keynote and education sessions, listen to global regulators during our Regulatory Round Table, interact with and learn from vendors about the latest and greatest new technologies and services in the exhibit hall, and attend numerous networking events during the conference.

I again encourage companies, vendors, affiliates, chapters, members, and company leadership to consider support for programs like the Student/Recent Graduate Grant in future years through donations to the ISPE Foundation. These students and recent graduates represent our future, and you can help influence their career decisions by enabling them to learn and see what the pharmaceutical industry is all about.

PE THEME: BIOTECH, C&GT, AND ATMPS

The pharmaceutical industry has come a long way in the 36 years since I started my career. In the late 1980s, small molecules dominated the product portfolios of pharmaceutical companies, and rDNA products were just beginning to be developed and approved by regulatory agencies around the globe. The biotech side of the industry was just beginning, and now has evolved to heavily dominate the development of new therapies for patients.

This issue is focused on biotech, cell and gene therapy (C&GT), and advanced therapy medicinal products (ATMPs)—topics that, quite honestly, I am far from an expert in and I've truly been amazed to see the innovative therapies that have resulted from advances in these areas. These therapies are based on genes, cells, or tissues delivered to patients to provide a therapeutic benefit, determined by a specific target of interest. For ATMPs, the therapy is a cell, engineered tissues, or the manipulation of the patient's genome.

ATMPs have been the focus of numerous PE articles, an ISPE guide (*Advanced Therapy Medicinal Products—Autologous Cell Therapy*), and conferences, including the 2023 ISPE Pharma 4.0™ and Annex 1 Conference 11–12 December 2023 in Barcelona, Spain, which has a dedicated track focused on Annex 1 ("ATMPs and Pharma 4.0™: How Do They Fit Together?"). I encourage you to attend and to learn more about this technology, which provides real promise for the future of patient therapies.

MY FINAL THOUGHTS

This is my last "Message from the Chair" column. It has been my real pleasure and an honor to serve as your International Board Chair. During the last year, I have had an even greater chance to interact with Affiliates and Chapters, leadership teams,

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Communities of Practice (CoPs), task teams, individual members, ISPE staff, and regulators. ISPE has also started to implement our 2023–2025 Strategic Plan.

Some significant highlights include making great strides on implementing our One ISPE program, which has enabled ISPE to successfully operate its worldwide business, achieve the ISPE vision and mission, provide an operating framework that fosters global growth, and enable synergistic value between ISPE International and the Affiliates and Chapters. This also included the approval and establishment of our 40th Affiliate/Chapter, the Southwest Chapter.

ISPE successfully partnered with Wiley to enhance our guidance documents portal, which significantly improves the online user experience for ISPE's full library of guidance documents, and launched a new ISPE website configuration, which improved our members' ability to find and use their member benefits. ISPE launched several new CoPs in 2022 and 2023, including Pharma 4.0™, Pharmaceutical Compounding, and Quality Control/Analytical, and is looking to establish other CoPs, including Sustainability and Artificial Intelligence (AI).

In the regulatory area, ISPE continued efforts associated with the drug shortage crisis. We released new guidance on prevention readiness in May 2023 and the ISPE Harmonization Initiative, Enabling Global Pharmaceutical Innovation: Delivering for Patients, was launched with the objective to "catalyze consistent and harmonized interpretation and implementation of ICH guidelines [1]." In addition, three guides on Advancing Pharmaceutical Quality (APQ) were published: Change Management (CM) System, Cultural Excellence, and Process Performance and Product Quality Monitoring System (PPPQMS).

These are just some of the highlights from 2022–2023. Thank you to those who have supported efforts like this—we are very much a volunteer organization and cannot be successful without the support and efforts of our members and the staff of ISPE. I passed the gavel to Scott Billman, the 2023–2024 International Board Chair, at the Annual Meeting, and now pass the "Message from the Chair" column to him as well. I know you are in great hands with him as Chair and look forward to supporting him in my last year on the Board as the Immediate Past Chair. Thank you again for your support and I, like you, look forward to another phenomenal year for ISPE in 2024.

References

1. International Society for Pharmaceutical Engineering. "Enabling Global Pharmaceutical Innovation: Delivering for Patients." https://ispe.org/initiatives/regulatory/enabling-global-pharmaceutical-innovation-delivering-patients

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By Vivianne J. Arencibia


Vivianne J. Arencibia

A LETTER FROM ISPE'S WOMEN IN PHARMA® CHAIR

We welcomed 2023 with high hopes and dreams of what Women in Pharma could eventually be. As I prepare to conclude my time as the Chair of ISPE's International Women in Pharma Steering Committee, I do so with immense gratitude.

ISPE members from disparate organizations worked together for years to create a framework that would create an unstoppable force within the pharmaceutical industry; a truly global community that would transcend the expectations of a female empowerment group and spark true change. The program was finally ready to turn these ideas into action, and if done right, Women in Pharma would become an integral part of ISPE's DNA.

Reflecting on this last year, I can confidently say we've accomplished just that. ISPE's Women in Pharma group has become the voice of diversity, equity, and inclusion for ISPE International, and through the efforts, passion, and commitment of our past and current International Steering Committee, Affiliates and Chapter leaders, and Woman in Pharma liaisons, we continue to drive programming on the global and local level, providing the education and tools necessary to advocate for oneself and others.

2023 HIGHLIGHTS

Women in Pharma closes out the year with over 2,100 members, a 50% growth in just three short years. Our journey is less than 10 years old, and yet the community continues to gain momentum and support from women and their allies.

We launched Mentor ISPE on International Women's Day (8 March 2023), welcoming over 240 ISPE members into the program. This innovative initiative connects pharma professionals around the world, matching them in groups of four. Each member brings a unique perspective, level of experience, and cultural background to the discussion groups, and each member can be both the mentor and mentee. We're concluding year one and preparing to match the groups for year two, expanding the experience from nine months to one year.

We hosted a session at each of ISPE's international conferences, two of which were live-streamed: "Advantages of Diversity, Equity and Inclusion, Sponsored by ISPE Women in Pharma," and "Tools for Success in a Multinational and Multigenerational Environment, Sponsored by ISPE Women in Pharma."

We hosted five webinars: "Unpromotable Work," "Workforce of the Future: Adjust Your Company Culture for Success," "How to be an Ally, Presented by AstraZeneca," the Mentor Match Party, and the Mentor ISPE Informational sessions.

We expanded our International Steering Committee to be truly multinational, reflecting the diversity within the ISPE Community, and the pharmaceutical industry as a whole.

Women in Pharma is made up of so many talented individuals, all of whom have found and contributed value to this evolving community.

A BITTERSWEET FAREWELL

As I prepare to conclude my time as the Chair of ISPE's International Women in Pharma Steering Committee, I do so with immense gratitude. It's been quite rewarding to have an opportunity to meet so many people, and to be in a position where I've been able to give back based on my personal experience while learning from everyone I've come in contact with. Women in Pharma is made up of so many talented individuals, all of whom have found and contributed value to this evolving community. It's bittersweet to say farewell, but I believe I leave it in good hands. I can't wait to see the impact Women in Pharma will have on our industry and the world.

Vivianne J. Arencibia is the Vice President of Global Quality Systems and Compliance with Moderna Therapeutics, Inc., 2022–2023 Secretary of the ISPE International Board of Directors, and 2022–2023 Chair of the ISPE International Women in Pharma Steering Committee. She has been an ISPE member since 1991.

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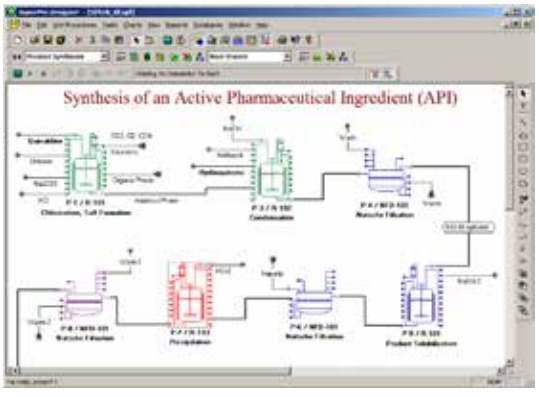

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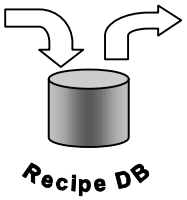

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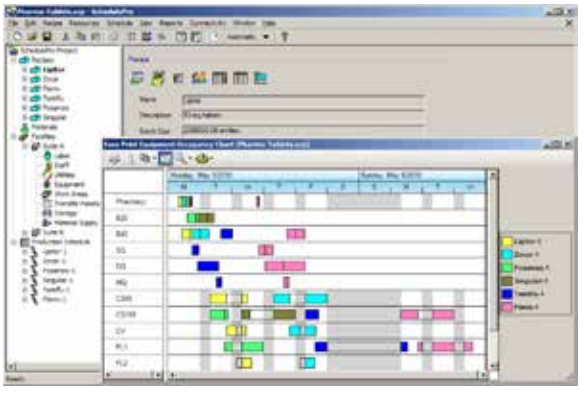

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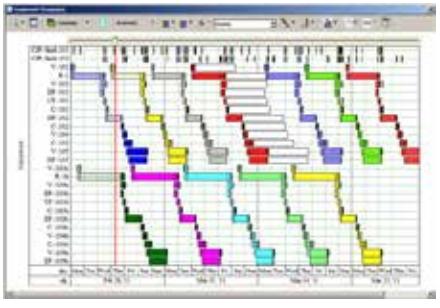

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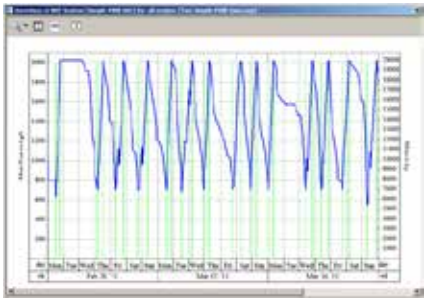

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SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, 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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By Zen-Zen Yen


Zen-Zen Yen

GROWTH THROUGH SERVICE: REFLECTING ON A YEAR ON THE BOARD

As my first year on the ISPE Board of Directors draws to a close, I find myself reflecting on a year filled with unprecedented learning, growth, and valuable insights.

Serving as a representative for Emerging Leaders and students on the International Board has been a transformative journey that has broadened my perspectives and has also significantly contributed to my personal and professional development. The experience of working with thought leaders in the industry with diverse backgrounds has allowed me to strengthen my knowledge and interpersonal skills.

GAINING INSIGHTS BEYOND BORDERS: A TRANSFORMATIVE JOURNEY

Stepping into the role of a board member for ISPE was a decision driven by a desire to contribute to a greater purpose. Little did I know that this experience would extend far beyond my initial expectations. One of the most remarkable aspects of this journey has been the exposure to the operations of a large global nonprofit in the pharmaceutical industry. Witnessing the orchestration of events, initiatives, and collaborations on an international scale has been eye-opening. It underscored the critical importance of compelling visions, effective leadership, clear communication, and strategic planning in driving the mission of an organization that spans continents.

During my tenure, I had the privilege of engaging with professionals from diverse backgrounds and cultures. This global perspective not only enriched my understanding of the challenges and opportunities facing the pharmaceutical industry, but also highlighted the universal nature of our shared goals. From regulatory harmonization to technological innovation, it became evident that the exchange of ideas across borders accelerates progress and fosters a sense of camaraderie among professionals worldwide.

BRIDGING PROFESSIONAL SUCCESS: LESSONS FROM A GROWING GLOBAL COMMUNITY

The lessons gleaned from my year on the ISPE Board of Directors have permeated every facet of my career. One of the most impactful realizations has been the power of collaboration. Working alongside accomplished individuals with varied expertise emphasized the significance of interdisciplinary cooperation. Just as the board brings together professionals from diverse fields, so does the pharmaceutical industry require the seamless integration of scientific, regulatory, and business perspectives.

Additionally, the experience showed me the importance of adaptability in an ever-evolving landscape. Navigating the complexities of a global nonprofit organization in an era of rapid change highlighted the need for agility and innovative thinking. The pharmaceutical industry, like ISPE, is beginning to operate more and more in a dynamic environment shaped by technological advancements, regulatory shifts, and societal demands. Embracing change rather than resisting it is a fundamental lesson that I will carry forward.

Furthermore, my interactions with fellow board members and industry leaders illuminated the essence of mentorship and continuous learning. Each conversation served as a wellspring of knowledge, offering insights that extended beyond my existing expertise. The willingness to learn from others, regardless of their position or background, has proven invaluable. It reinforces the notion that growth is a perpetual journey, and humility is the compass that guides us toward new horizons.

A JOURNEY OF GRATITUDE AND ANTICIPATION

As I bid farewell to my role on the ISPE Board of Directors, I do so with profound gratitude for the opportunities and lessons this experience has bestowed upon me. The past year has demonstrated that service to a global nonprofit organization transcends mere involvement—it is a commitment to contributing to a larger collective purpose. My journey with ISPE has been shaped by numerous volunteering opportunities made available to me, all thanks to the trust within the organization and the enthusiasm and engagement of the emerging leaders and students around me.

As I move forward, I firmly hold the belief that the valuable knowledge acquired over this transformative year will influence my personal and professional pursuits in the future. The lasting impression of ISPE's impact on me serves as a powerful reminder of what can be achieved through collaboration and united efforts toward a shared objective.

Zen-Zen Yen is Head of Engineering for Bayer AG and the 2022–2023 ISPE International Emerging Leaders Chair. She has been an ISPE member since 2016.

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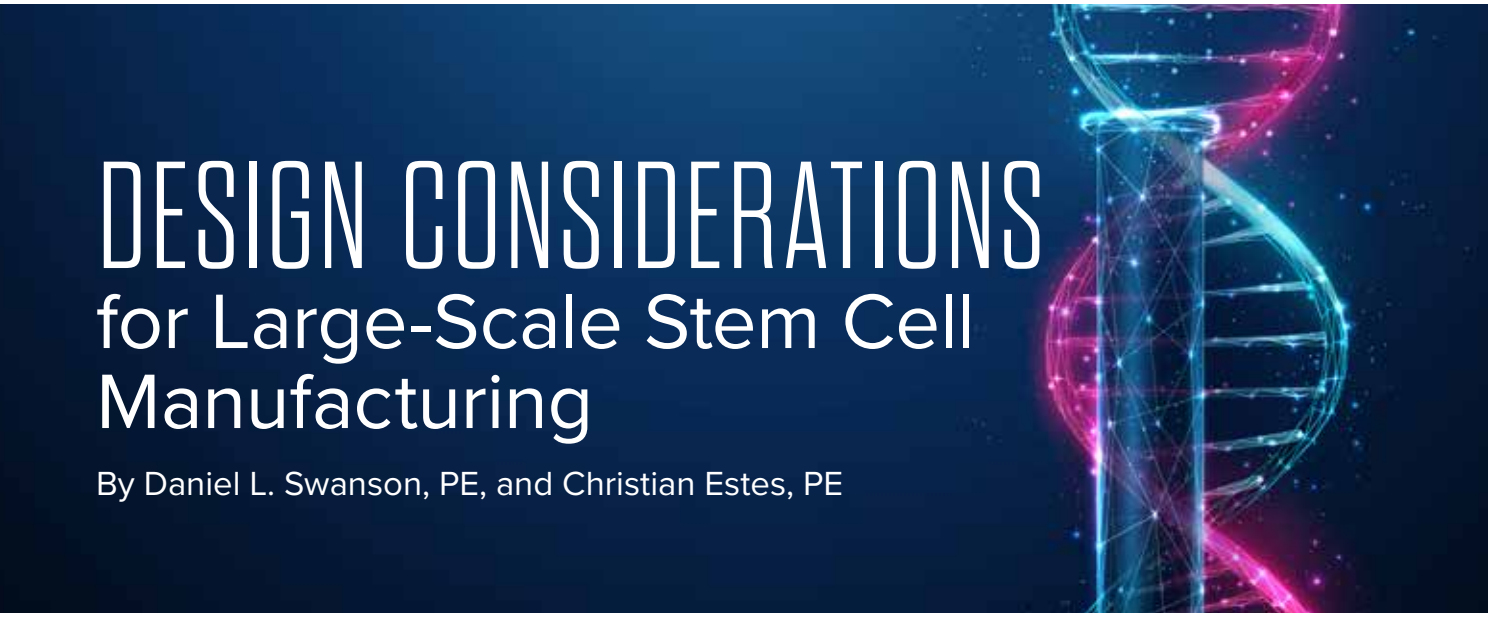

DESIGN CONSIDERATIONS for Large-Scale Stem Cell Manufacturing

By Daniel L. Swanson, PE, and Christian Estes, PE

There is much that large-scale commercial stem cell therapy processes can adopt from the existing bioprocessing industry. This article addresses some of the unique challenges posed by large-scale stem cell and stem cell–derived product manufacturing processes, and what should be considered while designing a manufacturing facility.

In 1931, Swiss surgeon Paul Niehans injected parathyroid cells from a calf embryo into a woman whose parathyroid gland had been partially removed by accident during surgery. Though his claims of multiple successful treatments of cancer using this technique have never been validated by research [1], his idea of using live cell products to treat patients spawned an industry that has produced many scientifically proven products.

As of Q2 2022, there were 59 nongenetically modified cell therapies approved for commercial use and an additional 803 in development globally [2]. This excludes ex vivo gene therapies such as chimeric antigen receptor T cells (CAR Ts) or T cell receptors (TCRs), which are often lumped together as "cell therapies." Nongenetically modified cell therapies generally fall under two umbrellas: autologous and allogeneic. Autologous therapies use a patient's cells as the starting material, whereas allogeneic therapies use donor cells.

There is a strong desire in the industry to move toward allogeneic cell therapies because they have several advantages over autologous cell therapies, including reduced cost to the patient, ease of automation, and ability to produce scalable "off-the-shelf" products. Nevertheless, allogeneic cell therapies face challenges to reaching commercial viability, such as the potential to induce graft-versus-host-disease (GVHD) and the risk of immune-mediated rejection by the host. Large-scale allogeneic stem cell manufacturing will become increasingly common as these challenges with GVHD are addressed, as the industry matures, and as indications with larger patient populations are targeted.

When it comes to manufacturing scale, allogeneic cell therapies currently being developed and manufactured are based on different modalities, which dictate batch size. Allogeneic CAR-Ts and natural killer (NK) cells are typically made at 10 to 50 L scale, but many stem cell and stem cell–derived drug products are targeting larger production capacity. The manufacturing scale is primarily triggered by patient dosing requirements and patient population size.

Cell dosing requirements for mesenchymal stem cell (MSC) or pluripotent stem cell (PSC) therapies are estimated to need up to 10^9 cells/patient, with some indications having anticipated market sizes needing hundreds of thousands of doses. It is anticipated that some commercial allogeneic stem cell manufacturing will require batch sizes in the 200 to 2,000 L range, producing 10^{11}–10^{14} cells/year for a single product to reach commercial viability [3].

THE START

The key to designing a stem cell or stem cell–derived product manufacturing facility is to address the multivariable problem of constraints, goals, adjacencies, and cost. The facility must be designed and built to promote simplified production by the operators, consider workflows, enable safe operation, and ease regulatory compliance. All manufacturing flow paths through the facility must be studied, including product, personnel, raw materials, waste, and equipment. Too much focus on the primary process can lead to insufficient study of support functions such as media preparation and delivery, kitting, quality control (QC) laboratories, or warehousing. Taking a broader view of the facility will allow for a more comprehensive design.

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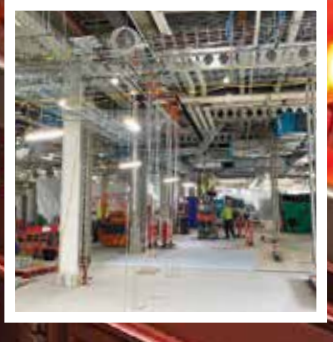

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OPEN VS. CLOSED

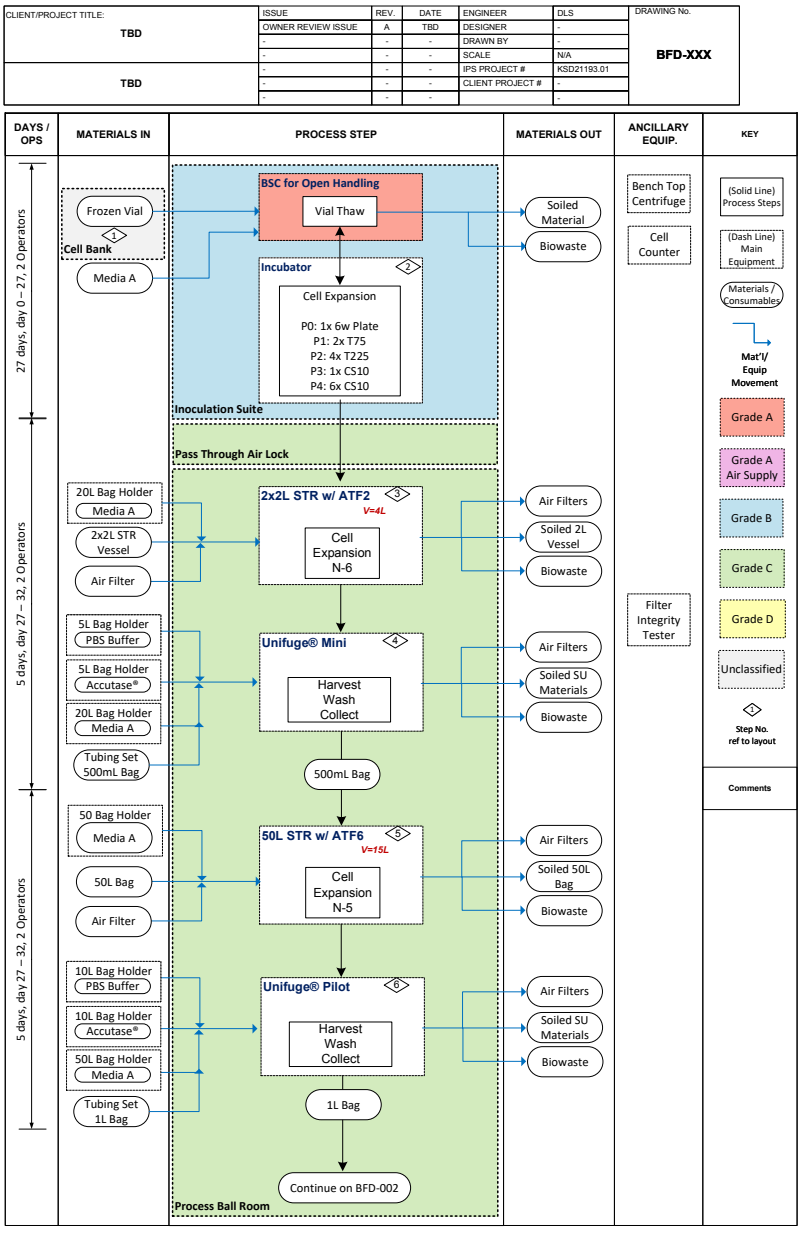
One of the biggest considerations when designing any biomanufacturing facility is whether the process is "open," "closed," or a mix of the two. Cells in an open process are exposed to the surrounding environment and the operators. Closed processes are designed such that the surrounding environment and operators are not exposed to the process or vice versa. This is accomplished using stainless steel vessels and piping, single-use systems and tubing assemblies, isolators, and other means.

Open processes have an inherently greater risk of contamination than closed processes and require a higher-grade environment and a more conservative facility design; thus, for streamlined facility design and optimum operator and product safety, closed processes should be considered wherever possible. Although parts of a process—such as a single-use bioreactor for cell expansion—may be closed, all processing steps—such as inoculation or harvest—must be considered during facility design. A block flow diagram (see Figure 1) helps identify each process step and assign an open or closed label. If a processing step is not currently closed, the means for "closing" it should be considered.

It is important to understand that stem cell products are living cells that cannot be sterilized by filtration, heat, or any other current method. Therefore, full aseptic processing is required from start to finish. There must be a focus on maintaining aseptic techniques to prevent the introduction, transmission, or spread of communicable disease from the outset of operations [4]. Because many stem cell processes start their development in academia or small research laboratories, there is a trend toward processes using many manual open steps to limit initial costs and ease operations. As these processes graduate to larger clinical trials or commercial manufacturing, early process development should focus on using closed processing and more automated procedures to lower the risks of contamination and improve efficiency.

Product development efforts should keep scalability in mind early during technology transfer implementation to ease this transition. By minimizing the amount of open processing required in the early stages of manufacturing, there is an opportunity for substantial savings in cost and footprint in both equipment and building utilities. Occasionally, a specific step in an otherwise closed process cannot be closed due to project timeline, cost, or other reason. In this scenario, a dedicated room and additional transition airlocks are likely required to segregate the open process. Open processing requires, at minimum, working in a biosafety cabinet (BSC) with a Grade A air supply in a Grade B room background [4].

Figure 1: Example of a block flow diagram.

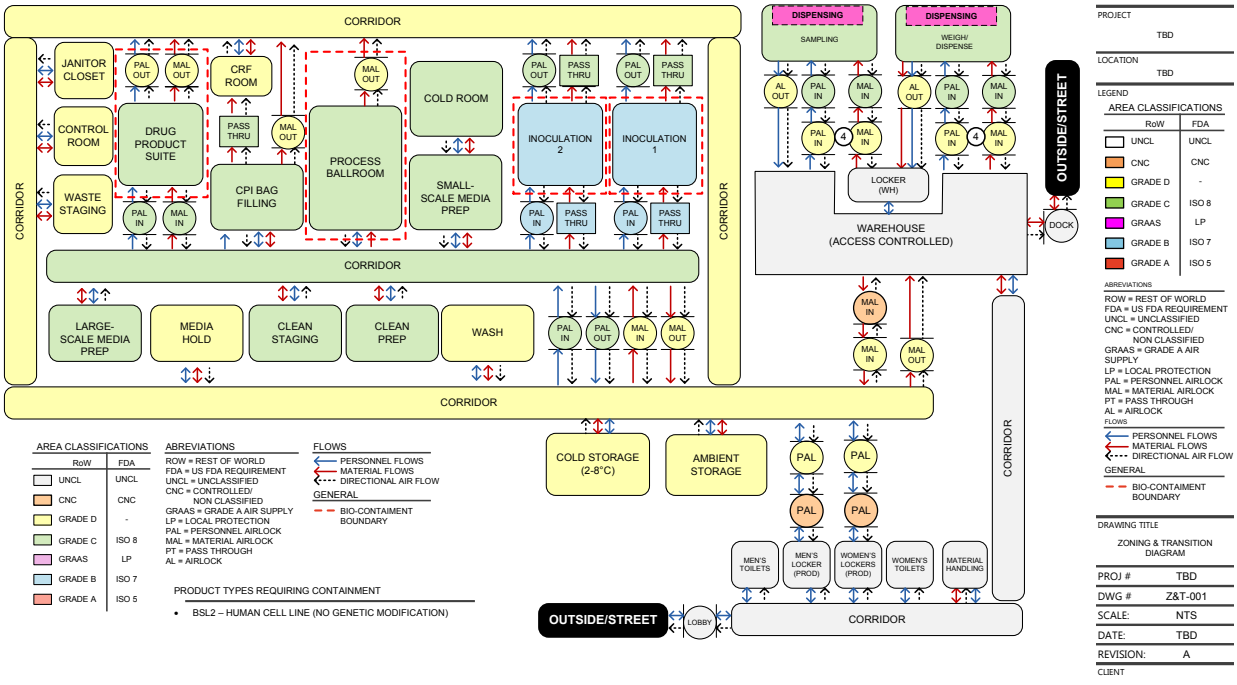


BSC: Biosafety cabinet
STR: Stirred tank reactor
SU: Single use
PBS: Phosphate-buffered saline
ATF: Alternating tangential flow filtration

RISK ASSESSMENT

Before a facility layout is developed, a set of preliminary risk assessments should be performed. Risk assessments relate to business, quality, and safety functions of an

Figure 2: Example of zoning and transition.



organization and are a requirement to meet Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH) guidelines [5]. Specific risk assessments can be performed for product contamination risk, process reliability (product loss), product cross-contamination risk (product to product, batch to batch), and environmental, health, and safety (EHS) risk. Zoning and transition diagrams (see Figure 2) are a great tool to understand potential adjacencies of different process manufacturing operations and can be used to facilitate a risk assessment. The risk assessment typically falls into one of the following categories.

Single-Product Facilities

The risk profile for single-product facilities is relatively low compared to other types of facilities. The focus of the assessment is typically on aseptic operation, batch segregation, and worker safety. Based on risk assessment, these facilities may be designed with bidirectional flows with proper airlock design for required material and personnel transitioning. Single-product facility designs often allow for consolidating multiple closed functions into a single room.

Multiproduct Facilities

Potential for cross-contamination increases in a multiproduct facility, so both facility design elements and operational elements must be considered. Individual products must have a designation and secure manufacturing sequence. Several means can be leveraged to reduce the risk profile, including campaigning, physical segregation, once-through heating, ventilation, and air conditioning (HVAC) design, and careful sanitization. *ISPE Baseline® Guide Vol 7: Risk-Based Manufacture of Pharmaceutical Products* [6] outlines a scientific risk-based approach for managing the risk of cross-contamination within multiproduct facilities.

Contract Manufacturing Organizations (CMOs)

CMOs often have special considerations due to the nature of their business, which involves insourcing other organizations' manufacturing operations. CMOs often have multiple clients, processes, and products housed under the same roof, and the multiproduct risks are magnified. This increased risk often becomes a concern for their clients and frequently drives a compartmentalized suite approach for phase II clinical trial manufacturing through commercial-scale manufacturing.

REGULATORY COMPLIANCE

Too often, it happens that the initial layout and concept designs are performed without fully considering the relevant regulations and guidelines. First, the markets in which the product will be sold must be defined. This will drive which good manufacturing practices (GMPs) the facility design must follow. Next, the location where the facility will be constructed must be established. This location will drive things like biosafety requirements, building code, and environmental and waste handling requirements. The following are some of the key regulations that constrain facility design and provide insight into the regulatory expectations.

United States

The following GMP regulations from the Code of Federal Regulations are relevant:

- 21 CFR Part 1271—Human Cells, Tissues, and Cellular and Tissue-Based Products [4]
- 21 CFR Part 210—Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General [7]
- 21 CFR Part 211—Current Good Manufacturing Practice for Finished Pharmaceuticals [8]
- 21 CFR Part 600—Biologics Products: General [9]
- 21 CFR Part 610—General Biological Products Standards [10]
- 21 CFR Part 11—Electronic Records; Electronics Signatures [11]

The following GMP guidelines from the US Food and Drug Administration should be considered:

- "Guidance for Industry. Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)." December 2011 [12]
- "Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice." September 2004 [13]

The following safety regulations are relevant:

- 42 CFR 73—Select Agents and Toxins Regulations [14]
- OSHA regulation, 29 CFR 1910.1030—Bloodborne Pathogens [15]

The following safety guidelines should be considered:

- CDC/NIH—Biosafety in Microbiological and Biomedical Laboratories (BMBL) 6th ed. [5]
- NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [16]
  - Small-Scale < 10 liters – Appendix G
  - Large-Scale > 10 liters – Appendix K (includes manufacturing)

Finally, the following federal, state, and local building codes, as well as other specific guidelines, must be addressed:

- International Code Council (ICC)
- National Electrical Code (NEC)
- Occupational Safety and Health Administration (OSHA)
- National Institute for Occupational Safety and Health (NIOSH)
- National Fire Protection Association (NFPA)
- Americans with Disabilities Act (ADA)

Europe

The following GMP regulations are relevant:

- Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) no 726/2004 [17]
- European Commission. "EudraLex, Volume 4: Good Manufacturing Practice—Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products." [18]
- European Commission. "EudraLex, Volume 4: EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use. Annex 1: Manufacture of Sterile Medicinal Products." [19]

The following biosafety regulations and guidelines are relevant:

- Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the Contained Use of Genetically Modified Micro-Organisms [20]
- Specific regulations and guidelines issued by EU member states

For building codes, specific regulations and guidelines issued by EU member states should be followed.

Rest of the World

Many countries, such as Canada, Brazil, China, and Mexico, have country-specific regulations and guidelines. Building codes are often country-specific.

The following GMP and biosafety regulations and guidelines may be relevant:

- Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme (PIC/S) PE-009-16 Annex 2A—Manufacture of Advanced Therapy Medicinal Products for Human Use [21]
- The World Health Organization (WHO) generally publishes GMP and biosafety guidance for countries that do not issue their own regulations or guidelines

Considerations

Although not all the regulations listed are relevant for every facility, the engineers and architects designing the facility need to understand which aspects are critical. The recent update to EU GMP Annex 1 (2022) [19] has added the requirement for facilities to have a contamination control strategy (CCS). While regulators have always expected facilities to have a documented plan to control contamination, existing approaches may not always be coordinated between different departments (e.g., QC, quality assurance, or manufacturing), leading to disjointed data from original qualifications, validations, process controls, and environmental monitoring.

Additionally, corrective and preventive actions taken in response to deviations and trend analyses may lack both integration into a comprehensive strategy and a link between critical control points and evaluations of control effectiveness (design, procedures, technology, and organization) [22]. However, a holistic view is proposed in Annex 1 (2022) [19] for particulates, microbial, and pyrogen contamination. There is still discussion and debate around exactly how CCSs should be developed and documented. With that said, the ECA Task Force on Contamination Control Strategy has created the guideline "How to Develop and Document a Contamination Control Strategy," which should serve as an excellent starting point [22].

Figure 3: Stem cell manufacturing unit operations.

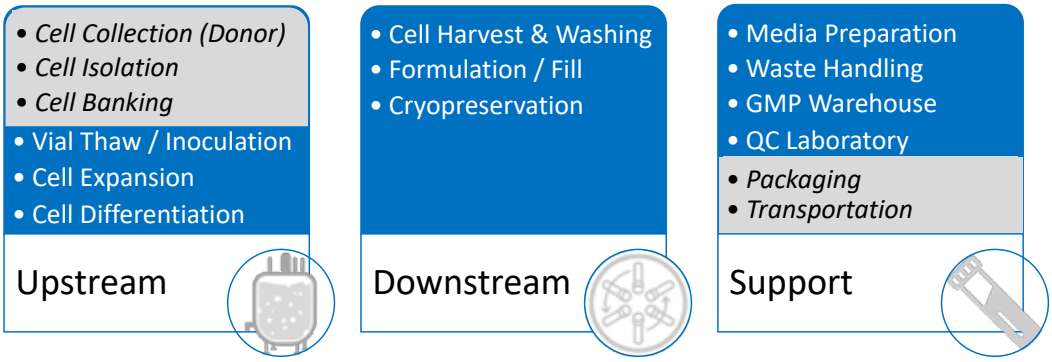


Table 1: Inoculation economic analysis: isolator vs. biosafety cabinet in Grade B suite.

Category	Time	Biosafety Cabinet	Isolator	Comments
Capital Costs				
Capital Facility	Initial cost	$ 533,600	$ 413,000	Estimated $/sq ft
Capital Equipment	Initial cost	$ 119,571	$ 1,117,550	From equipment quotes
Install	Initial cost	$ 8,500	$ 78,500	Soft cost allowance - 7% of capital
Commissioning	Initial cost	$ 8,500	$ 316,650	Soft cost allowance - 7% of capital + vendor-supplied commissioning costs
Maintenance Costs				
Maintenance	Annual	$ 14,500	$ 67,500	Soft cost % of capital
Labor Costs				
Manufacturing Operators	Annual	$ 300,000	$ 300,000	$150,000 per full-time equivalent operator (2 operators)
Cleaning Labor	Annual	$ 150,000	$ 75,000	$150,000 per full-time equivalent operator (2 and 1 operators)
Operational Costs				
Heating, Ventilation, and Air Conditioning	Annual	$ 136,207	$ 37,196	
Environmental Monitoring	Annual	$ 150,000	$ 75,000	Assumed value
Gowning Materials (Grade B)	Annual	$ 103,181	$ -	
Gowning Materials (Grade C)	Annual	$ 93,683	$ 93,683	

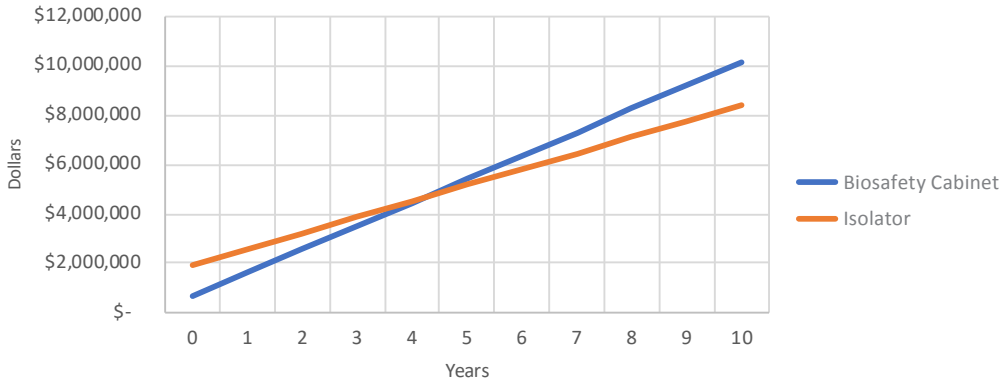
OPERATIONAL CHALLENGES

To better understand the challenges posed by large-scale stem cell and stem cell–derived product manufacturing, it is easiest to review the operations found in most stem cell processes and facilities (see Figure 3). The list of considerations is certainly not all-encompassing, but it should provide a strong overview of the major challenges. The manufacturing of stem cells begins with donor selection, but this article focuses on the manufacturing facility starting with inoculation. Cell line development—including cell collection, cell isolation, cell activation, or cell banking—is considered outside of the scope of this article.

Inoculation

In most applications, initial vial preparation requires manual and open processing, necessitating a Grade A environment. This environment can be achieved in a couple of ways, either by using BSCs with a Grade B background or within an isolator in a Grade C or Grade D background, depending on the regulatory environment

Figure 4: Isolator breakeven analysis.



(EMA vs. FDA). Although isolators provide the most qualifiable sterile environment, the choice between the two methods usually falls into a debate over cost, schedule, operational flexibility, and risk associated with batch loss.

At the time of writing, the most common choice is to perform inoculation in a BSC with a Grade B background. BSCs have the benefit of process versatility, whereas isolators are better suited for mature processes due to the need for customization. Often overlooked is the fact that Grade B space can become very expensive in both capital and operation costs when architectural finishes, HVAC, gowning, cleaning, and turnover time are considered. Some studies (see Table 1 and Figure 4) have shown that isolators, while often having a higher capital cost, can have a relatively short breakeven period when considering costs over the lifetime of the equipment. Ultimately, this should be investigated on a case-by-case basis when designing a facility.

Cell Expansion

Selecting the right scalable platform for stem cell expansion can greatly affect facility design. Although there are technologies available that can be adopted for stem cell manufacturing from existing bioprocessing standards, the specific requirements for stem cell processes should be carefully reviewed and addressed before using existing solutions. Many stem cell lines are being developed using traditional adherent plate flatware, such as T-flasks and multilayer cell culture vessels. While some autologous or small-scale allogeneic processes may use flatware for commercial production, this is not feasible on a large scale due to the operational challenges of increased equipment size and complex automation.

Alternatively, many of the commercially available closed adherent bioreactors have been developed with gene therapy or other traditional biologic products in mind, where the products are expressed extra-cellularly, or the cells are lysed to recover intracellular products. Harvest of live cells poses a major challenge in many of these adherent platforms due to the type of substrate that is used as an anchor for the cells. There are some commercially available adherent platforms with substrates designed to allow for high yield and viability while harvesting live cells, but these platforms are not yet available in the capacity required for large-scale manufacturing. With that said, these platforms could serve as a useful seed train design solution to close the expansion operations as early as possible in the process.

Given the current technology, suspension-based approaches for adherent stem cells, typically coupled with perfusion technology for continuous media exchange, have proven to be more scalable. The two current methods are microcarrier-based suspension and cell aggregate suspension. Microcarrier suspension uses microporous beads or other media that allow adherent cell lines to attach and grow in high density while suspended within a liquid medium.

This approach allows the use of commercially available and proven scalable suspension bioreactors but introduces an additional process operation. To harvest cells that are adhered to microcarriers, the cells must first be dissociated from the beads. This is typically performed with the addition of a dissociative agent, such as trypsin. After the disassociation, the beads then also need to be separated from the cells. This is typically done via some form of filtration. Alternatively, aggregate suspensions are an acceptable growth method for some stem cell lines, wherein groups of cells form colonies or aggregates to support growth while in suspension.

Monitoring and controlling the cell density and aggregate formation is key in these processes to maximize cell growth and viability. In addition, cells will periodically require disassociation methods between interim growth expansion steps to allow for fresh aggregate formations in new media or transfer into final product formulation.

Stem cell culture processes and stem cell line development are not yet mature; thus, process development to support an increased number of stem cell passages poses many challenges. Given this, options for reaching large-scale production may be limited. Facility designs will likely need to have considerations for both scaling up and scaling out to reach production targets. If developing a stem cell process for a single large production bioreactor is

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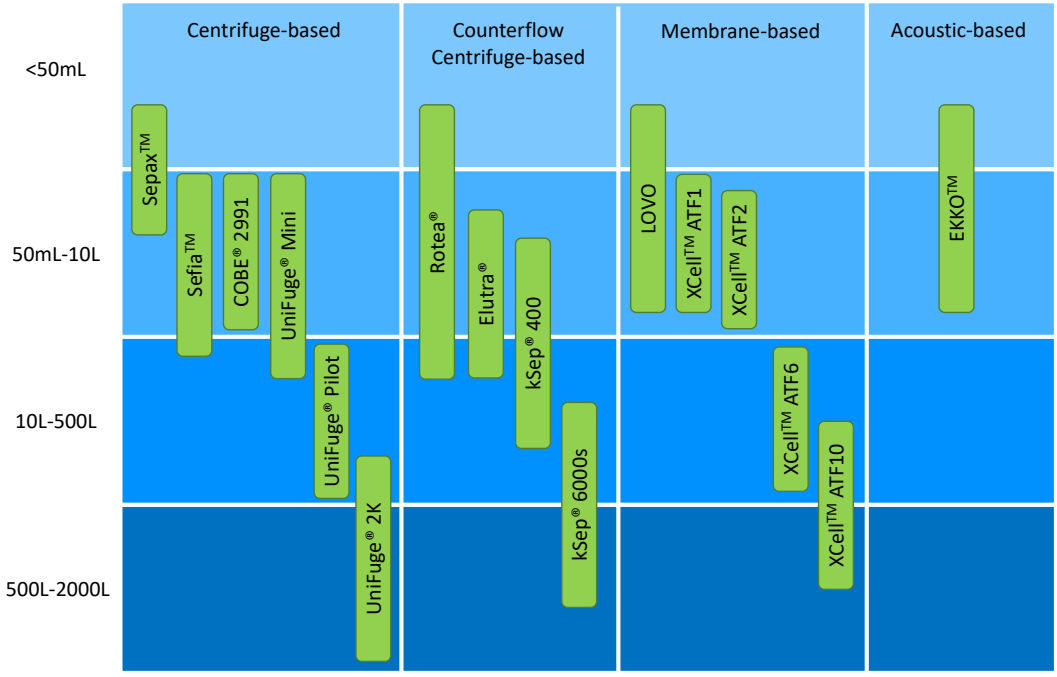
Figure 5: Single-use cell harvest technology [23].



not possible, the facility may need to support a process that has multiple smaller reactors.

Cell Harvest and Washing

A key area where stem cell manufacturing differs from traditional biotech is harvest and purification. Traditional biotech may use a combination of centrifugation, depth filtration, chromatography, tangential flow filtration (TFF), or other forms of filtration to remove cell debris or target a specific protein, whereas stem cell harvesting typically has fewer unit operations. The target of stem cell harvesting is to collect individual live cells. This can be completed by a series of operations, including dissociation (if necessary), quenching, washing, concentration, and collection.

As a cell product, every harvest step requires a focus on critical quality attributes such as cell concentration, total cell count, and cell viability. The cells themselves must be maintained in good condition throughout the operation, limiting equipment choices for wash and concentrate operations where there is potential for high shear forces or other damaging impacts to the cell product. To choose the correct operating methodology and equipment, each process step requiring the manipulation of the product volume and composition must be closely investigated to find the most appropriate solution.

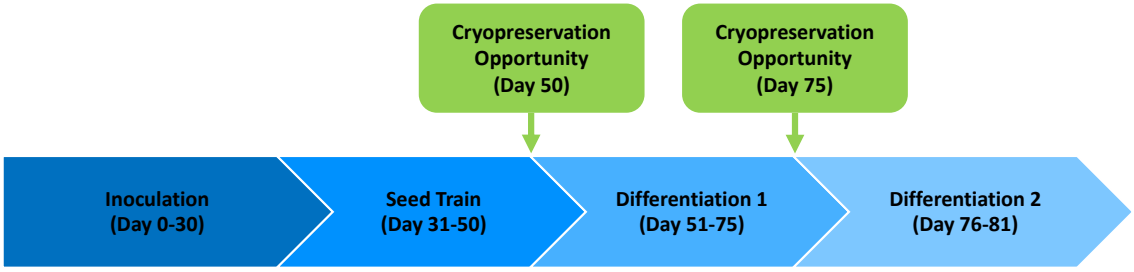
Beyond the harvest process, other operations may require adjustments to cell concentration. Many stem cell expansion processes require regular media exchange to replenish nutrients and remove cell waste byproducts. This media exchange can be done continuously (perfusion) or via discrete media exchange where the working volume in a bioreactor is reduced and a bolus of media is added. This type of media exchange can improve cell density and overall health.

Stem cell–derived products may require many different specialized media types to be added discretely. This discrete media exchange can be necessary to direct cell differentiation into the desired pathway. Each of these steps necessitates the removal of spent media and the introduction of new media to the product liquid without negatively impacting the product cells. The choice of technologies that results in maximum processing rates and volumes can greatly benefit the overall manufacture of these cell products.

There are several technology platforms used for cell harvest or media exchange, but not all can meet the needs of large-scale manufacturing (see Figure 5). Single-use equipment options are the leading solution to this design challenge and include centrifugation, acoustic wave separation, TFF, and alternating tangential flow (ATF) filtration (see Figure 4). Acoustic wave separation is an interesting and promising technology, but it is not commercially available for large-scale manufacturing.

Although TFF or ATF may be appropriate for continuous media exchange, the throughput of these systems is typically too slow for discrete media exchange or harvest operations. Presently, single-use centrifugation is the most effective solution for cell harvest or media exchange. It allows for dissociation, quench, wash, concentration, collection, and discrete media exchange all with the same piece of equipment with relatively short processing times. Designing processes to use the same piece of equipment for

Figure 6: Intermediate cryopreservation strategy example.



multiple unit operations can allow for a smaller facility footprint, higher equipment utilization, and reduced capital cost.

FORMULATION, FILLING, AND CRYOPRESERVATION

Some large-scale stem cell processes require multiple types of filling technologies and formats for intermediate and final products. Given the long timelines for cell expansion and differentiation at large-scale, it can be advantageous to strategically decouple operations by cryopreserving and storing intermediate products. Decoupling operations such as seed trains and production bioreactors can reduce the impact of a batch failure and ease batch scheduling.

Consider, for example, a process that has a failure during the differentiation phase. If that process has a cryopreservation operation directly before differentiation, differentiation could be restarted immediately using the cryopreserved intermediate, losing only a week or two of productivity (see Figure 6). A process that does not have an intermediate cryopreservation step would have to start from a vial from the primary cell bank, losing several weeks or months of productivity.

Filling and cryopreservation of most cell therapy products is a small-scale operation. The cells are formulated with a cryoprotective agent, such as 10% dimethyl sulfoxide (DMSO), to prevent the formation of crystals during freezing. The formulated product is then filled into a small number of cryovials or cryobags. The cryoprotective agent can affect cell viability if kept in a liquid state for extended periods, so the formulation step starts a "freeze window" that is typically one to two hours. The cryovials or cryobags are then transported to a benchtop-controlled rate freezer where the vials or bags are brought down to the target temperature using liquid nitrogen. This operation is adequate for most existing cell therapy manufacturing processes, but large-scale stem cell therapy processes require large-scale solutions.

To improve logistics and material handling, it can be advantageous to fill and freeze intermediate products in larger formats than traditionally done in cell therapies (i.e., 500 mL and larger). Consider an instance where a differentiation bioreactor requires 4 L of cryopreserved intermediate to inoculate. It is far easier for operators to handle four 1-L bags, or even one 4-L bag, during the thawing and inoculation process than twenty 200-mL bags. This same logistic and material handling challenge is encountered during freezing. It is much easier to move a smaller number of larger bags from a filling operation to a freezing operation than it is to move a large number of small bags.

Most automated technologies available for filling bags in the 200 mL to 5 L size range are isolated high-speed units designed for intravenous (IV) fluids. These isolated high-speed filling lines are designed to fill at a minimum of 500–1,000 bags/hr. This capacity would be excessive for most stem cell therapy products and comes with a high capital cost and large footprint. Another option to a traditional high-speed bag filling line is a closed, single-use, manifold-style filler.

A growing number of vendors are tailoring their filling products to cell therapy processes, and there are now a handful of vendors that have single-use manifold-style offerings fit for 50 mL to 20 L bags. One of the challenges of using a larger bag format is that there is little to no publicly available data on post-freeze cell viability. In the short term, manufacturers will have to generate their own experimental data to prove the large-scale technology is capable of freezing intermediate products without large cell loss.

Media Preparation and Delivery

Media is an essential component of all cell culture processes, but supplying media to large-scale stem cell processes can pose some unique challenges. These challenges can come from both the stem cell process and the composition of the media itself. Some of the major challenges posed by the process include sterile preparation, large process scale, continuous perfusion requirements, bolus media additions, and preparation and delivery of several types of growth and differentiation mediums.

Because the final cellular product cannot be filtered in a sterile fashion, the entire process, including media production, must be performed in a sterile (i.e., not bioburden-controlled) fashion. This means additional filtration and testing is required compared to a traditional biomanufacturing process and could drive the need for larger or dedicated QC laboratories. Small-scale cell therapy processes can leverage external suppliers to provide preprepared sterile liquid media in single-use containers.

The sheer volume of media required for large-scale stem cell processes makes purchasing preprepared media impractical and

Table 2: GMP warehouse storage requirements.

Storage Type	Ambient	2°C–8°C	–20°C	–190°C
Storage Basis	6 months	4 months	12 months	12 months
Storage Unit	Pallet	Pallet	23 ft^3 freezer	750 L liquid nitrogen freezer
Quantity	700	120	10	12

thus onsite preparation from powdered media stock is necessary. Stem cells are notoriously media hungry, and some stem cell processes require continuous perfusion of media to sustain the cells. Continuous perfusion could mean an entire reactor volume is turned over every day of the process. Cell expansion and differentiation processes can both last several weeks, potentially requiring more than 10,000 L of media to complete a single 200 L production reactor drug substance batch.

Delivery of media from the preparation equipment to the bioreactors can pose additional challenges, making the development of a robust media delivery strategy essential. One of the biggest decisions is whether single-use or stainless steel media preparation and delivery equipment will be used or whether a combination of the two is required. One strategy to consider is using single-use media preparation and delivery equipment for the lower volume seed train while using stainless steel media preparation and delivery equipment for the larger product or differentiation bioreactors.

A typical media system would include a media preparation tank or single-use mixer, a sterile filtration skid or tubing set, a media hold tank or single-use tote, and a distribution system or tubing set. An analysis of capital and operating costs for single-use vs. stainless steel equipment can help inform the development of the media strategy. The chemical stability of the media, especially the chemical stability of any growth factors or small molecules, could drive the need for cold storage or limit the window between preparation and expiration. The need for a bolus addition of media to a bioreactor when switching between differentiation media types may mean cold media (2°C–8°C) needs to be warmed to 37°C before it is added to the reactor.

Unique strategies and schedules may have to be developed for processes that use multiple production or differentiation bioreactors. Take, for example, a process that uses four 500-L differentiation bioreactors. Each bioreactor could have a dedicated set of media equipment, or a larger batch of media could be prepared, held, and distributed to all the bioreactors. If cold storage and bolus media additions are required, then heat exchangers need to be added as part of the distribution to warm the media before delivery to the bioreactors.

BIOWASTE HANDLING

Human cell lines are considered to be potentially infectious and within the scope of the OSHA Bloodborne Pathogens Standard (BPS) unless the specific cell line has been characterized to be free of recognized bloodborne pathogens [24]. Additionally, the BMBL recommends that human cells should be handled using Biosafety Level 2 (BSL-2) practices and containment [16]. These biosafety implications are important when it comes to handling waste because waste handling procedures must adhere to the results of a site-specific risk assessment. The following recommendations are typical and assume the only biohazards are human stem cell products without genetic modification.

Solid Waste

All contaminated solid waste from the production area shall be decontaminated in accordance with applicable local, state, and federal regulations. This decontamination can be performed onsite or offsite as long as it is packaged correctly for transport [16].

Waste Flows

Designated waste flows should be considered for contaminated waste within the facility layout to avoid any source of cross-contamination. As a best practice, waste flows should be unidirectional and segregated from other material flows wherever possible. Where waste flows cannot be segregated physically, they should be segregated by time. Once the decontamination is complete, the waste can be moved to a central treatment area where a combination autoclave/shredder unit can be used to treat the material, which can then be disposed of as municipal solid waste. Alternatively, if biowaste hauling services are available at the site, the biowaste cart can be moved to a waste storage area for offsite treatment.

Liquid Biowaste

Large volumes of liquid biowaste generated in Grade C or Grade D cleanrooms should be collected via a dedicated, fully welded biowaste drain system in the GMP rooms. If the drain system is located underground, double-contained piping with active leak detection should be considered. Although only required as part of BSL-3 design, as a best practice, the drain system should use closed connections/covers and drain vents that are outfitted with 0.2 µm or HEPA-grade filters to maintain a closed boundary and prevent the release of any airborne organisms. The waste can then be treated via a qualified decontamination method. This can be performed either chemically or thermally. The thermal option is a more conservative and flexible approach, and two system designs are typical: dual batch (using two alternating tanks for batch operations) or continuous decontamination.

The impact of the biological oxygen demand (BOD) of the liquid waste streams on the site waste permit should also be considered. For large-scale stem cell manufacturing facilities that use perfusion or regular discrete media exchange, large volumes of barely spent media (i.e., high-BOD waste) could be designated for the sanitary sewer. The BOD content of the waste should be analyzed and compared with the site permit limits. If necessary, the facility may require a means for segregating and collecting the high-BOD stream for hauling by tanker truck and treatment offsite.

GMP WAREHOUSE AND MATERIAL STAGING

Large-scale stem cell manufacturing facilities require significant and diverse storage space. Large amounts of short-term storage and laydown spaces are required in the clean core for staging single-use materials. For the GMP warehouse, ambient storage is required for single-use components and other shelf-stable materials. Storage at 2°C–8°C and –20°C is required for powdered media and other raw materials, respectively. Cold rooms would likely be required to support the amount of 2°C–8°C storage required, whereas –20°C storage may be able to be supported by upright freezer units. Cryogenic (–180°C) dry-phase nitrogen dewar storage is required for cryopreserved intermediate material. Table 2 displays an example of GMP warehouse storage requirements for a large-scale stem cell therapy facility.

QUALITY CONTROL LABORATORY

Large-scale stem cell manufacturing facilities require significant analytical support. The extensive amount of process sterility testing necessitates QC laboratory space to be located with access from the clean core for ease of sample delivery. QC laboratories also face the same biowaste handling requirements as the manufacturing area.

Although some stem cell drug products may be cryopreserved, others may need to be delivered to the clinic fresh (i.e., 2°C–8°C). The latter scenario requires very tight timelines from completion of filling to delivery to the clinic, similar to an autologous facility and product supply chain. Tighter product delivery timelines lead to ultra-fast release testing and drive the need for increased in-house capabilities. The QC area design should consider the ability to receive and test samples for the following:

- Product
- Media sterility/bioburden
- Raw materials
- Facility utilities monitoring
- Environmental monitoring
- Aseptic process simulation
- Revalidation — clean-in-place (CIP)/sterilization-in-place (SIP)/cleanroom

Additionally, space requirements in the QC area for equipment to support the following assays should be considered:

- Bioburden and sterility – endotoxin (LAL), mycoplasma (PCR), BACT/ALERT, Gram stain
- Biological indicators – growth
- Markers/purity/potency – nuclear/cytoplasmic markers, incubation, ELISA immunocytochemistry, high content imagery
- Karyology – G-banding/cytogenetic
- Content – hemocytometer, total count, viability
- General – appearance, conductivity, osmolality, pH
- Total organic carbon (TOC) – rinse water and swabs
- Environmental monitoring – total particulate, nonviable particulate, airborne viable particulate, surface viable particulate
- Gases and raw materials – identity

CONCLUSION

As single-use process equipment continues to evolve, there will be new opportunities to apply principles from the existing bioprocessing industry to the large-scale cell therapy field. Designing these facilities is a complex system of challenges based on safety, cost, and efficiency that requires leveraging constantly evolving technology. Doing so while meeting the needs of regulators, manufacturing, QC, facilities, and business units requires a team with the right expertise and experience.

References

1. "Unproven Methods of Cancer Management. Fresh Cell Therapy." *CA: A Cancer Journal for Clinicians* 41, no. 2 (1991):126–28. doi:10.3322/canjclin.41.2.126
2. American Society of Gene and Cell Therapy. "Gene, Cell, & RNA Therapy Landscape: Q2 2022 Quarterly Data Report." ASGCT.org. Accessed 1 December 2022. http://asgct.org/publications/landscape-report
3. Pigeau, G. M., E. Csaszar, and A. Dulgar-Tulloch. "Commercial Scale Manufacturing of Allogeneic Cell Therapy." *Frontiers in Medicine* 5, no. 233 (2018). doi:10.3389/fmed.2018.00233
4. US Food and Drug Administration. "21 CFR 1271 – Human Cells, Tissues, and Cellular and Tissue-Based Products." Updated July 2023. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271
5. Meechan, P. J., B. Hatcher, and J. Potts. *Biosafety in Microbiological and Biomedical Laboratories.* 6th ed. US Department of Health and Human Services. Public Health Service Centers for Disease Control and Prevention. National Institutes of Health. 2020. Accessed December 2022. https://purl.fdlp.gov/GPO/LPS124402NIH
6. International Society for Pharmaceutical Engineering. *ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP). Updated July 2017.*
7. US Food and Drug Administration. "21 CFR 210 – Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs: General." Updated June 2023. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=210
8. US Food and Drug Administration. "21 CFR 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals." Updated June 2023. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211
9. US Food and Drug Administration. "21 CFR 600 – Biologics Products: General." Updated June 2023. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=600
10. US Food and Drug Administration. "21 CFR 610 – General Biological Products Standards." Updated June 2023. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=610
11. US Food and Drug Administration. "21 CFR 11 – Electronic Records; Electronics Signatures." Updated June 2023. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11
12. US Food and Drug Administration. "Guidance for Industry. Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)." December 2011. www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-tissue-practice-cgtp-and-additional-requirements-manufacturers-human-cells-tissues-and
13. US Food and Drug Administration. "Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice." Published October 2004. www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice
14. US Department of Health and Services. "42 CFR 73 – Select Agents and Toxins Regulations." March 2005. www.ecfr.gov/current/title-42/chapter-I/subchapter-F/part-73
15. US Occupational Safety and Health Administration. "29 CFR 1910.1030 – Bloodborne Pathogens." Updated July 2001. www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1030
16. US National Institutes of Health. "NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules." Published April 2019. https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf
17. The European Parliament and the Council of the European Union. "Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) no 726/2004." Published November 2007. www.legislation.gov.uk/eur/2007/1394/contents#
18. European Commission. "EudraLex, Volume 4: Good Manufacturing Practice—Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products." Published November 2017. https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en
19. European Commission. "EudraLex, Volume 4: EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use. Annex 1: Manufacture of Sterile Medicinal Products." Published August 2022. https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf
20. The European Parliament and the Council of the European Union. "Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the Contained Use of Genetically Modified Micro-Organisms" Published May 2009. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:125:0075:0097:EN:PDF
21. Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme. "PE-009-16 Annex 2A—Manufacture of Advanced Therapy Medicinal Products for Human Use." Published February 2022. https://picscheme.org/docview/4590
22. ECA Foundation. "How to Develop and Document a Contamination Control Strategy. Version 2.0." ECA Task Force on Contamination Control Strategy. December 2022.
23. Li, A., G. D. Kusuma, D. Driscoll, N. Smith, D. M. Wall, B. L. Levine, D. James, and R. Lim. "Advances in Automated Cell Washing and Concentration." *Cytotherapy* 23, no. 9 (2021):774–86. doi:10.1016/j.jcyt.2021.04.003
24. US Department of Labor. "Standard Interpretations: Applicability of 1910.1030 to Establish Human Cell Lines." Occupational Safety and Health Administration. Published 21 June 1994. www.osha.gov/laws-regs/standardinterpretations/1994-06-21

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DELIVERING CURATIVE THERAPIES: Autologous vs. Allogeneic Supply Chains

By Pinar Cicalese, PhD, and Niranjan S. Kulkarni, PhD

Advanced therapy medicinal products (ATMPs) are one of the most promising developments in the pharmaceutical and biotech industries in recent decades. Although there is a great promise to treat and even cure many diseases with these products, there are also unique challenges, especially with their supply chains.

ATMP supply chains face substantial challenges related to scale-up and scale-out, timely deliveries, and costs. Supply chain costs represent approximately 30% of the total cost of treatment [1]. When designing efficient supply chain networks, it is critical to ensure best practices with sample tracking, package and shipping, storage solutions, software solutions, regulatory, trade compliance, customs regulations, and chain-of-custody documentation.

Cell therapy products are a subset of ATMPs. Cell-based products can be damaged due to mishandling, leading to contamination or loss of functionality. They are sensitive to temperature and stress, requiring special care and expertise in handling during transportation. These products can be classified as autologous or allogeneic depending on their starting cell origin. In this article, we explore some commonalities and differences between autologous and allogeneic supply chains.

AUTOLOGOUS SUPPLY CHAINS

This patient-centric supply chain starts and ends with the same individual (patient). A typical autologous supply chain is shown in Figure 1. In supply chains, one of the most important metrics is lead time, which is usually defined as the time when a customer places an order to the time that order is shipped or received: from receiving patient related raw material(s) to when the customer receives the order, including converting it to a finished product, packaging, and shipping. In autologous supply chains, this lead time is also referred to as vein-to-vein or needle-to-needle time because the input material comes from the patient and the final product is administered to the same patient.

As shown in Figure 1, the autologous supply chain starts with patient material and is supplemented by other raw materials, such as vector, media, and consumables. The patient material will typically be drawn at a clinical site. However, scheduling the procedure can be equally challenging. There is a need for real-time and efficient communication among all parties involved: clinics, manufacturers, and suppliers. These interactions improve the prediction of product delivery date based on the current manufacturing capacity, which allows manufacturers to level load their resources [2] and benefits patients by reducing the turnaround time.

The complexity of interaction between parties in these supply chain networks exceeds the interactions in supply chain networks of other existing industries due to the critical nature of the product being manufactured and shipped. After drawing the patient material (e.g., through apheresis), the patient material is packaged and shipped, either fresh or frozen, to the manufacturing centers. These materials are manipulated at the manufacturing site. The finished product is packaged and shipped either to a distribution center or directly to the clinical site for administration to the patient.

ALLOGENEIC SUPPLY CHAINS

An allogeneic supply chain starts with donor cells and ends with the product being delivered to another individual (patient). A typical allogeneic supply chain is shown in Figure 2. In allogeneic

Figure 1: High-level illustration of an autologous supply chain.

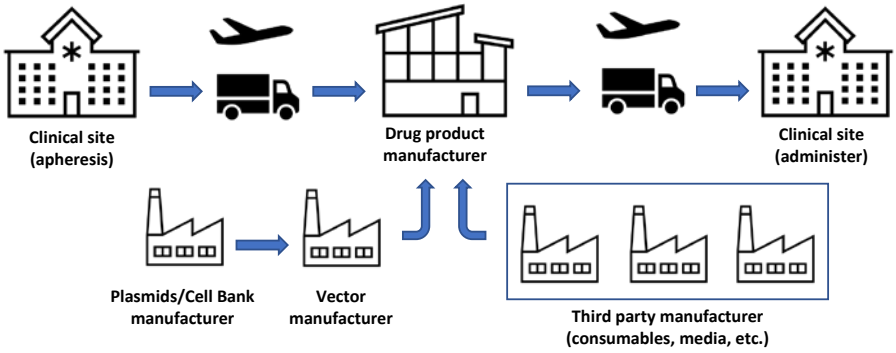
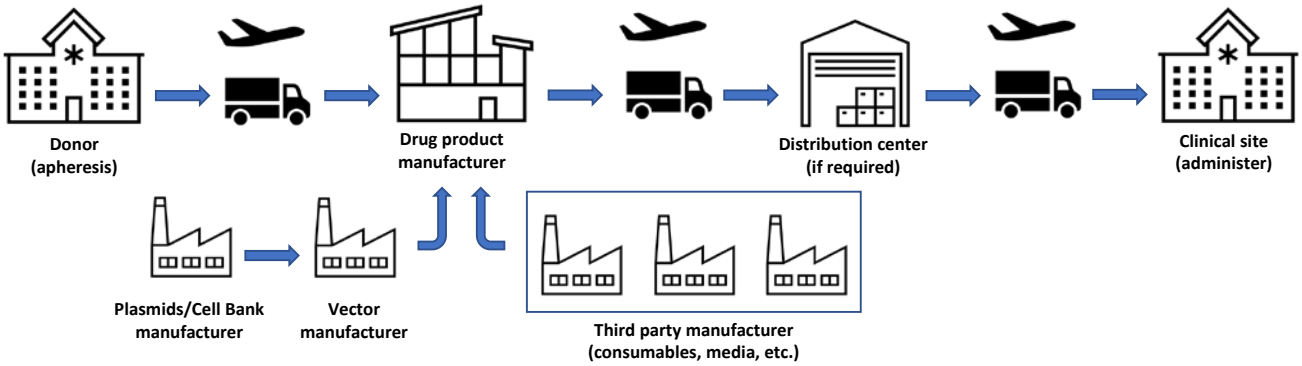


Figure 2: High-level illustration of allogeneic supply chain.



supply chains, securing consistent donor material is the key to ensure manufacturing robustness. Donor cells supplemented by other raw materials, such as vector, media, and consumables, are required to start manufacturing the drug product.

The donor material will typically be drawn at a certified clinical site or a blood donation center. Handling this material is a critical part of the supply chain. It's a complex process that includes finding appropriate donors and developing a strong donor pipeline; performing the apheresis; packaging transporting, and cryogenically shipping (as necessary) the donor material; implementing software solutions; and following regulatory, trade, and customs compliance.

Although a typical allogeneic therapy is conceived as off the shelf or make to stock, there are many other types of allogeneic therapies that may require other approaches to distribution of the drug product. The supply and distribution strategy needs to be aligned with the product and clinical needs. Universal make-to-stock therapies would allow a more traditional push model (i.e., a model where the product is placed upstream in the supply chain where it is required) for distribution in a temperature-controlled (cold) chain.

If there is a requirement for the donor to be matched in the ABO blood group system or by human leukocyte antigen (ABO/HLA) type, the manufacturer may need to maintain an inventory of multiple batches from varying ABO/HLA type donors. Maintaining inventories for these products would be more complex, but the product still would be make-to-stock. If the therapy has a very short shelf life, the drug product needs to be made to order, as in case of autologous therapies. However, as the donor material acquisition is decoupled from the patient, the turnaround time for the therapy may be reduced or manufacturing slot planning may be easier.

KEY SIMILARITIES

Input Materials

Autologous and allogeneic cell therapies have similar input materials, such as cells, vectors (if cells are genetically modified), cell growth media, media additives, excipients for final formulation, and consumables. In both types of therapies, the starting cell

population will need to be transformed (if cells are genetically modified) and expanded to produce the desired dose of the drug product.

Manufacturing for both therapies can start with fresh or frozen cells. Fresh cells can introduce further complexity to the manufacturing process because they need to be transported within a very limited timeframe (usually up to 72 hours, unless qualified otherwise) to the manufacturing location from the collection center. This limited timeframe can pose challenges during unexpected logistics interruptions (such as weather-related events or strikes in any part of the logistics chain).

It is important to have multiple logistics options and backup plans when using fresh cells as starting material. Starting with frozen cells is easier for manufacturing schedule because it provides the flexibility to accommodate any logistics or manufacturing delays. If the cells are frozen at the collection or apheresis center, it is important to devise clear standard operating procedures for centers to follow and to have a training plan.

In allogeneic drug product manufacturing, unless the shelf life of the product is prohibitively short, the goal is to manufacture multiple doses of the product. Thus, the scale and time frame of cell expansion, the volumes of reagents used, and the types of consumables may differ. However, the approach and management of the supply chain for the input materials (excluding cells) will remain the same. These materials can be ordered ahead of time and a certain level of strategic stock can be managed. Single-sourced raw materials are common in ATMP manufacturing and stocks should be managed accordingly.

As the number of patients going through clinical stages into commercial manufacturing increases, the supply chain may need to plan for sizable inventory, set service level agreements with existing vendors, or identify and validate a secondary source or vendor to avoid interruptions in manufacturing. The inventory will depend on patient treatment frequency, supplier lead times, and availability of alternative raw material. It is recommended to consider these alternative raw material options (if available) during initial process design or regulatory filing stages because it may be more costly and time consuming to make changes later.

Vector supply can be planned according to the patient forecast. Unlike many of the other inputs, the materials vector will be unique for each product; thus, stock management and planning for the long release times due to certain safety testing, e.g., replication competent lentivirus (RCL) is important. Supporting vector stability studies to claim as long of a shelf life as possible will make supply planning easier.

Warehouse Management

Because each batch produced in autologous therapy manufacturing is for a unique patient, the amount of raw material turnover may be faster. Though allogeneic therapy manufacturing can produce more doses, the batch sizes are much smaller than in traditional biopharmaceutical manufacturing, such as monoclonal antibodies. Subsequently, for both therapies, challenges associated with small-batch manufacturing—increased material handling and flow, inventory turns and associated cycle counts, labor hours required for pick and place activities—can be anticipated.

In both autologous and allogeneic therapies, the approach to warehouse management can follow the same principles. The raw materials received undergo an incoming quality inspection, including a visual inspection and phase-appropriate sampling and testing. The materials are held in a quarantine status until being released by the quality department. The raw material may need to be removed from the incoming packaging (wooden pallets, corrugated containers, etc.) and stored in plastic boxes or totes.

Kitting—the process of collecting parts and components per the bill of materials (BOMs) into a single kit—can be performed in advance of the production dates to simplify manufacturing operations. Appropriate kit expiration dates should be considered based on the raw materials being kitted.

Warehouses follow the appropriate engineering design factors, such as temperature and humidity monitoring and control and the proper air circulation between racks and stored materials. The layout should be designed to optimize material and personnel flows.

Packaging and Shipping

Almost all autologous and allogeneic therapies require freezing the drug product at cryogenic conditions and the use of cold supply chains to reach the patient. Packaging and handling products that require dry ice or liquid nitrogen shippers necessitate special considerations such as dedicated rooms for packing, exhaust, and monitoring. Special packaging and preparation as well as additional paperwork may be required if the product will be transported by air.

The packaging system may go through mechanical-, thermal-, or pressure-related stresses during the shipment. Thus, when designing the operational and performance qualifications, these stresses are considered and modeled carefully. The cryogenic temperatures that the packages may have to withstand could render the packaging materials brittle and may create failure points in shipments. Therefore, simulations of extreme conditions as well as actual transport conditions are covered during shipping qualifications.

It is important to include temperature monitors in the shipments; to have the proper placement of monitors; and to have the ability to start, receive, and download data from the monitors. Tamper-evident devices are also used as part of the qualification. Mock shipments for each shipping lane are recommended to troubleshoot any unforeseen circumstances.

Labeling for any products that are stored or shipped in cryogenic conditions needs to withstand these harsh conditions. Labels, as well as label ink, need to withstand a wide temperature range, e.g., from 37°C to the vapor phase of liquid nitrogen. Similar to the packaging systems, a special qualification for labels for abrasion and adhesion at the actual usage temperature, storage, and shipping conditions will prevent future deviations. For content development of labels, please refer to the widely endorsed

global standards for terminology, identification, coding, and labeling of medical products of human origin, ISBT 128 [3].

Waste Handling

Waste management should also be given its due importance. Given the batch size of the one-per-patient philosophy, typically higher volumes of waste are generated for autologous therapies. Although the amount of waste created may be different for autologous and allogeneic cell therapies, the general principles of waste handling and management would remain the same.

Waste generated in manufacturing, packaging, quality control (QC), warehousing activities, or any other areas of the facilities are moved out in a timely manner. Appropriate staging space for waste should be allocated in the facility. Process waste, packaging waste, biowaste, etc. are handled per the company policy and local environmental policies and laws. Proper segregation of waste from drug product or raw material is achieved through physical or temporal segregation and developing and adhering to standard operating procedures.

KEY DIFFERENCES

Input Material: Donor vs. Patient

ATMP input materials and challenges posed by these materials are more complex compared to large molecule pharmaceuticals. Some of the input materials, such as cell growth media, media additives, or excipients for final formulation, may be similar to biopharmaceuticals. The most important input material is the donor material (in the case of allogeneic products) or the patient material (in the case of autologous products).

Donor material

Finding the right donor pool is very important. However, acquiring donor material has its own challenges due to factors such as donor eligibility, donor deferral, different motivators and barriers to donor recruitment, and decreased trust in the health care system, to name a few [4]. Furthermore, even for the eligible donors, there may be variability between the donor material (though it may not be as significant an issue as experienced in the autologous therapies). As demands for these therapies increase or there is a surge in receipts of donor material, upstream cold and frozen storage requirements should be carefully scrutinized.

In addition to the challenges of finding the right donor pool, there are concerns with the donor material itself. Immune rejection can be a concern. Haploidentical matching and other human leukocyte antigen–related concerns need to be addressed. Safety, efficacy, and durability for allogeneic cell therapies is yet to be proven widely [5]. However, these may become less of a concern as more therapies emerge, e.g., Ebvallo™ (tabelecleucel), which was approved as an allogeneic T cell immunotherapy.

Furthermore, because donor material can result in a product that can go to multiple patients, the screening and testing of donor materials is tightly controlled by regulatory authorities [6]. For example, apheresis blood products or mesenchymal stem cells from bone marrow are governed in Europe by the EU Blood Directive 2002/98/EC 27 [7] and the EU Cells and Tissues Directive 2004/23/EC [8], respectively, and in the United States by 21 CFR 1271 Subpart C Donor Eligibility [9].

The donor material needs to be tested for multiple communicable agents such as human immunodeficiency virus types 1 and 2, human T cell leukemia virus types 1 and 2, hepatitis B virus (HBV), hepatitis C virus (HCV), West Nile virus (WNV), and Zika virus. Furthermore, such requirements can depend on the regulatory agency's region and jurisdiction. For example, differences exist in the expectation of the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan with regard to the list of viruses of concern and testing periods compared with those given by the European Medicines Agency (EMA) and the US FDA [6].

A robust donor pipeline is key for business continuity in allogeneic supply chains. The planning process should include all process steps and control points across the entire supply chain. Risk assessments should be generated and updated periodically as data becomes available.

Patient material

The most critical input material—patient cells—is a source of great variation. A patient's age, genetic background, or state of disease can make these cells more robust or vulnerable to certain types of treatment. Sometimes the patient has gone through multiple rounds of prior line treatments such as chemotherapy and the cells can be fragile or more prone to have challenges in manufacturing. Thus, the process for ATMPs needs to be more robust to accommodate the inherent variability in the incoming patient material.

Scheduling patients has its own challenges. Scheduling is typically done manually, especially in the early stages of development. A significant amount of coordination is required between clinics and manufacturing sites with available capacities. When scaling up, adding more resources may not be economical. Effective IT systems will be important and in conjunction with the logistics systems, available data can be used to automate and forecast upcoming requests.

Variability in the arrival rate of the incoming patient material also poses a challenge for manufacturing schedules. This variability is more pronounced for fresh cells because the cells arriving at the manufacturing center have only a very limited amount of time (usually 24 hours) to be further processed. Therefore, the manufacturing center needs to always have a certain capacity available to handle this variability on arrival. This can mean overtime, 24/7 coverage, or need for additional resources for the manufacturing center.

Manufacturing: Scale-Out vs. Scale-Up

Within manufacturing, the most critical unit operation is the modification and expansion of cells. Automated and closed systems can help control and manage the process. As demand for such treatments increase, that process must be scaled as well. For autologous therapies, the process needs to be scaled out with

multiple platforms and workstations, each making a single drug product for one patient (batch size of one). This may translate into the need for a larger workforce, more equipment, and more space. Whereas for allogeneic therapies, the lot size can be much larger. These therapies can be used to treat hundreds of patients. This scaling up to produce larger quantities that can be aliquoted into multiple doses to treat several patients is one of the advantages of allogeneic therapies.

The manufacturing time frame is also different for these two therapies. For autologous therapies, the vein-to-vein time (lead time) is critical because there is a life (patient) waiting at the other end. Usually, the manufacturing lead time is about two to three weeks. Uncertainties arising due to varying demands, possible sourcing issues and lead times for key raw materials, variability in the quality of patient material, arrival rate of patient material at the manufacturing center, and equipment reliability, to name a few, can influence the lead times and manufacturing costs of goods.

Rightsizing resources under these variable and uncertain conditions is very important to manage lead times and the costs of goods. Rightsizing involves estimating equipment, personnel, utilities, site logistics (material and personnel movement), spaces for production, raw materials, intermediate and finished goods staging, and support functions (e.g., warehousing, quality assurance (QA) and QC, maintenance, administration) [10]. Capacities should be planned to allow for surge demand when the schedules for the incoming patient material and outgoing patient therapeutics create a spike in workload.

The ATMP products are usually cryopreserved at the final stage of manufacturing and must be quarantined until all QA/QC procedures are completed and the product is released. Especially for autologous therapies, the QA/QC turnaround time becomes critical. As autologous therapies scale out, the number of samples to be tested can increase significantly. It is important to ensure that the labs do not become a bottleneck.

Because the vein-to-vein time for autologous therapies can be a few weeks, the patients must wait for a while. This makes maintenance of patient's health or consolidation therapies important to ensure the patients can receive those cells. The time between evaluating whether the patient is eligible and the infusion can be months. That changes in the case of allogeneic therapy, where infusion can occur in a matter of days [5]. With allogeneic therapies, there usually is less of a time constraint because a large batch can be produced in advance so treatment can be more readily available. However, for time-sensitive allogeneic therapies, i.e., when shelf life or hold times are shorter, their manufacturing process may look similar to autologous therapies.

Storage and Logistical Considerations

Although the storage and logistics attributes between the two therapies remain the same—the need for cold chains; packaging, shipping, and labeling considerations; sample storage; distribution challenges; chain of custody; strategies that include processes and procedures for the return and destruction of product, in compliance with the FDA, EMA, and other regulators—their scales are different. A few key differences are further explained next.

Cryopreservation is an important factor to be considered before and during shipping final products for both therapy types. Because autologous therapies cater to the same patient (have a batch size of one), the number of doses required to be frozen before shipment is not large. On the other hand, allogeneic therapies require larger storage capacity because one batch can be worth thousands of doses for multiple patients rather than a single dose per patient. Cryopreservation of large number of doses requires specialized equipment. Also, it is important to decide if the cryopreservation can happen in the same suite or adjacent suites.

The number of samples that need to be stored is higher for autologous therapies, including starting material from the patients, the final drug product, and everything in between. This may necessitate larger storage space or different storage strategies. In autologous therapies, the patient and their location are known from the outset. Although managing this cold chain is challenging, the distribution can be more complex for allogeneic therapies. The latter can be distributed to patients across a wide geographic area. This presents a unique challenge for the allogeneic therapies: identifying where to position product inventory, inventory quantities at these locations, and distribution channels for delivery to an undefined network of caregivers, all while maintaining product quality and service level agreements.

Universal make to stock is typically what people think of for allogeneic therapies and would allow a more traditional push model for distribution under a cold chain. A hospital orders, or has a standing order for, a therapy and the hospital may maintain a stock, like most other medicines. In the made-to-order approach, a pull system is employed, which requires coordination with the manufacturer's production slots. This model is usually adopted for autologous therapies. However, the front end is decoupled from the patient so an inventory of work in progress is typically maintained to reduce time from order to delivery. The made-to-order strategy may be applicable for allogeneic therapies with a very short shelf life or in the case of a large number of donor matched types (e.g., multiple-point HLA match).

To ensure patient and product safety and reduce human errors, a well-designed tracking system covering chain of custody and chain of identity is necessary. When developing or selecting the tracking system, ensure it can accomplish all needed tasks, such as linking geographic tracking data, monitoring temperature, and tracking and documenting chain-of-custody data in real time. Traceability may not be as critical in allogeneic supply chains as it is in the autologous supply chains. Orchestration plays a significant role in the autologous supply chains. However, chain of custody is important in both cases to ensure patient safety and product quality. Collaborating with relevant players in this chain of custody to share information can provide the flexibility to balance fluctuations in supply and demand.

Table 1: Summary of key similarities and differences.

Attributes	Autologous	Allogeneic	Points to Consider
Starting cell material	Patient	Donor	Allogeneic: Business continuity and securing donors
Chain of custody	Yes	Yes	
Chain of identity	Yes	Yes	Autologous: More critical for this therapy
Manufacturing expansion	Scale-out	Scale-up	Autologous: Facility design implications
Sample storage space need	Higher	Lower	Autologous: Facility design implications
Availability of treatment	Patient waits	Potential shorter patient wait time	Autologous: Maintenance of patient's health or consolidation therapies
Supply chain model	Pull (made to order)	Push (make to stock)	Allogeneic: If the therapy has a short shelf life, it may need to be made to order
Drug product inventory	Not available (unless multiple doses can be manufactured at once and can be readministered)	Available	Allogeneic: Evaluation of drug product inventory quantity and locations

The individualized nature of cell and gene therapy products also requires meticulous tracking of the patient material and final products. Maintaining identity and custody at each step of the supply chain is critical to ensure patient safety. Each therapy product should be tracked to the patient and the chain of custody should be visible to coordinators. Investing and adopting the right level of automation strategy is important to achieve this capability.

CONCLUSION

The curative promise of ATMP products makes them highly attractive solutions for certain diseases. However, managing supply chains where the patient or donor is a critical part of the supply chain can be challenging. Key similarities and differences have been described at a high level (see Table 1), but other aspects should also be considered when designing a robust supply chain.

Several steps in the supply chain are vulnerable to external issues like weather-related disruptions, macroeconomics, global political scenario, and raw material availability. Thus, supply chain mapping, exceptions planning, what-if analysis, corrective actions, and escalation protocols become important. These can help improve supplier relationships, manage overall costs, and, most importantly, save lives.

The level of automation and digitalization in manufacturing processes and supply chains should also be explored. An economically feasible and regulatory compliant digital roadmap that allows for tracking, collecting, and sharing or reporting the right data should be developed. The data-tracking equipment and protocols that suffice in the ATMP research lab may not be transferable to a commercial-scale, GMP-grade aseptic manufacturing environment. An ATMP facility might receive and release thousands of product batches over the course of a year. These facilities, and their supply chains, will need robust strategies to prevent product mix-ups and ensure the integrity and traceability of every one of those batches, including samples sent to the QC labs.

Clinics and hospitals are also an integral and crucial part of the ATMP supply chains. It is important to ensure trained staff is available at these sites for apheresis, as well as when the product arrives and is ready for administration. Appropriate equipment and processes for thawing, washing (if required), and administering should be available at these sites.

The complexity of the ATMP supply chains is unique. These supply chains involve clinics, transportation partners, third-party material providers, manufacturers, and biopharmaceutical and biotechnology companies. Partnerships for all supply chain players are also complex: There are scheduling and logistical challenges; issues controlled by contracts and confidentiality agreements, training programs, and significant amounts of documentation that often are specific to individual hospitals. The supply chain challenges are considerable, and it is never too early to start addressing them, especially when the goal is to deliver the curative power of these therapies to the patients at the end of these supply chains.

References

1. Franco, C., and A. L. Edgar. "Optimization Under Uncertainty of the Pharmaceutical Supply Chain in Hospitals." *Computers & Chemical Engineering* 135 (2020):106689. doi:10.1016/j.compchemeng.2019.106689
2. Wang, K., et al. "A Multiscale Simulation Framework for the Manufacturing Facility and Supply Chain of Autologous Cell Therapies." *Cytotherapy* 21, no. 10 (2019):1081–93. doi:10.1016/j.jcyt.2019.07.002
3. International Society of Blood Transfusion (ISBT 128), Technical Documents, Cellular Therapy, https://www.isbt128.org/technical-documents. Accessed June 2023.
4. Shaz, B., and C. Hillyer. "Minority Donation in the United States: Challenges and Needs." *Current Opinion in Hematology* 17, no. 6 (2010):544–9. doi:10.1097/MOH.0b013e32833e5ac7
5. Pike, R., D. Motlagh, and P. J. Hanley. "Autologous Versus Allogeneic: The Future of Manufacturing and Standardization in Cell Therapies." *Cell & Gene Therapy Insights* 8, no. 7 (2022):1083–95. doi:10.18609/cgti.2022.162
6. Apte, A., A. Afuwape, Z. Buljovcic, and Z. Younges. "Manufacture and Regulation of Cell, Gene, and Tissue Therapies Part 1: Chemistry, Manufacturing, and Control Challenges." *BioProcess International* 18 (2020):6–12.
7. Publications Office of the European Union. "Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 on Setting Standards of Quality and Safety for the Collection, Testing, Processing, Storage and Distribution of Human Blood and Blood Components and Amending Directive 2001/83/EC." *Official Journal of the European Union, L Series* L 033 (8 February 2003):0030–40. https://eur-lex.europa.eu/LexUriServ/
8. Publications Office of the European Union. "Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells." *Official Journal of the European Union,* L Series L 102 (7 April 2004):0048–58. https://eur-lex.europa.eu/LexUriServ/
9. US Food and Drug Administration Center for Biologics Evaluation and Research. "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products. Guidance for Industry." August 2007. www.fda.gov/media/73072/download
10. Kulkarni, N. "Cell and Gene Therapy Facility Design Using Simulations." *Pharmaceutical Engineering* 40, no. 6 (November/December 2020):12–15.

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OPTIMIZING COST OF GOODS for Cell Therapy Manufacturing

By Jeffery Odum, CPIP

Facility design decisions made early in conceptual design can have a significant impact on the cost of goods sold (COGS) in the manufacture of autologous and allogeneic cell therapy products. Understanding the impact of a COGS analysis is an important aspect of the early-phase design process.

For most cell therapies, emphasis is placed on the cost of starting materials, the protection and control of the supply chain, and the efficiency of manufacturing to support rapid cell processing. These requirements are discussed in detail within the content of the *ISPE Guide: Advanced Therapy Medicinal Products (ATMPs) Autologous Cell Therapy* [1]. Organizations beginning the journey into clinical manufacturing will focus on the key topics outlined in the guide's section on manufacturing, including process understanding around unit operations, equipment selection, and process control. But what about the COGS?

"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 cell therapy products (CTPs) is often driven by factors related to development, clinical manufacturing logistics, and facility optimization. Since 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" [2, 3].

"Specific factors to consider include analytical testing, operational attributes, product protection strategy, manufacturing logistics, and technology solutions" [3, 4]. A number of factors impact COGS, including direct costs (labor, materials, and sampling); indirect costs (operating costs, consumables, and testing); and amortization/depreciation costs (facilities, equipment, and third-party services). Addressing these factors can produce significant data options for consideration during conceptual design.

METHODOLOGY

"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. 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" [3].

"The key is to have a tool that will provide the necessary data for evaluation while also making the data accessible during the design phase of the project. As design attributes change, so will the data. The tool should be user friendly and easy to implement" [3]. Figure 1 provides a visual example of how a decisional model can be created.

"The inputs required to evaluate manufacturing costs would include personnel requirements; unit operational data; batch size; operational scale; qualification data; and materials and consumables.

For early-phase design development, the focus is on defining the established fixed costs that can be supported with available data, including:

- Equipment sizing/vendor data: In the model process, all unit operations are performed in single-use components. This is driven by scale of operation, flexibility, and level of automation. For this model, unit operations are assumed to remain manual-focused during the clinical manufacturing phases, consistent with many operations producing chimeric antigen receptor T (CAR T) cell products today. Key information would include product protection via biosafety cabinet (BSC)/isolator; cell processing via cell enrichment and cell washing; concentration; filling; and cryo storage.

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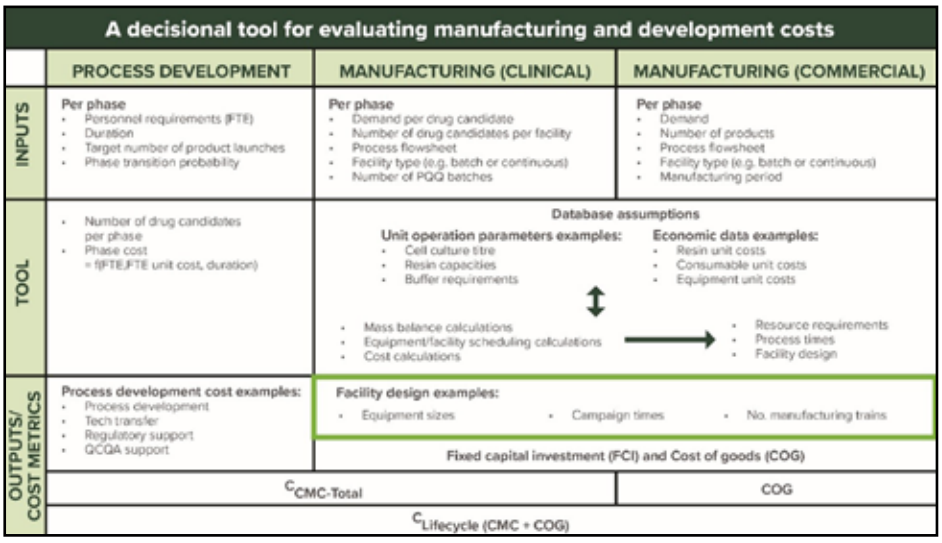
Figure 1: Sample decision model [5].



- Utility consumption: Load calculations based on facility attributes (heating, ventilation, and air conditioning unit sizing/zoning) and average energy cost (localized).
- Area sizing/classification: Energy usage intensity and operations schedule.
- Consumable costs based on target manufacturing outputs: Bags, micro beads, bottles, pipettes, and tubing.

There will also be a need to identify key assumptions necessary to complete the COGS model: batch targets based on manufacturing time durations; testing requirements; headcount, measured in full-time employees; energy costs; annual maintenance costs; and scaled facility costs (tax rates)" [3].

TOOLS

The tools that evaluate different production scenarios to aid in compiling costs depend on accurate data, or valid assumptions that cover the necessary cost model attributes. These tools can be either manual worksheets that use macros to automatically adjust data entry on a cell-by-cell basis in the spreadsheet or computer-generated models.

The key to success in generating numbers that have meaning and validity is the strength of the data input; "garbage in, garbage out" truly applies. Some examples:

- Equipment costs based on actual purchase price or validated bid price
- Accurate energy costs in dollars per kilowatt hour ($/kWh) based on actual monthly bills
- Mass balance volume accuracy for each unit operation
- Consumables costs: Equipment and personnel assigned units
- Sampling: Environmental monitoring and process costs and frequency
- Materials: Volume and cost per unit

Data entry must be specific and accurate. A worksheet tool would include items such as:

- Item type: Equipment type, price, and quantity
- Materials: A description of each line item
- Base UoM: The unit of measure for each item in the purchasing unit, e.g., ea. (each), L (liter), or g (gram)
- Purchase amount: Quantity purchased based on unit of measure
- Purchase price: Cost of each item purchased based on unit of measure
- Unit of measure quantity per patient: Quantity of the unit of measure used for each patient.

USE OF THE TOOL

To show the use of a tool focused on design input, a CAR T clinical/launch facility will be used as a model. In this basic model, the facility has the following set of operational attributes defined and included as factors during conceptual development: a focus on CAR T CTPs; phase 1, 2, and 3 clinical manufacturing; Grade A BSC in Grade B background classification basis for manufacturing; a 15-year amortization period; consistent average energy cost ($/kWh) for utility costs; and annual taxes and maintenance costs. A phased expansion approach to meet increasing manufacturing demands for clinicals will include manufacturing and support spaces. In phase 1, 15,000 sq. ft. will be used, followed by 45,000 sq. ft. in phase 2, and 90,000 sq. ft. in phase 3.

For the equipment platforms, the facility has the following set of operational attributes defined and included as factors during conceptual development: consistent unit operations through all phases of clinical manufacturing; equipment pricing based on current quotes within the last 12 months; operations classified as

"open" requiring Grade B classification; facility designed to allow for equipment additions as phasing dictates (phase 1, 30 campaigns annually; phase 2, 40 campaigns annually; and phase 3, 50 campaigns annually); and a 10-year amortization period.

The supplies required are estimated on a per-patient basis for the following: consumables, raw materials, gowning, cleaning, environmental monitoring, and storage and shipping. Personnel inputs are based on the defined CAR T process design and target production output for defined patient populations for each study phase. The focus of the model is on production, compliance, and supervisory personnel. The factors include compensation rates for salaried and hourly personnel, two eight-hour shifts per day, and a general factor for benefits based on compensation.

RESULTS

For this model, which implemented a manual tool, the request was to define a per-patient COGS estimate for each clinical phase, based on the following patient populations: 60 patients in phase 1, 600 patients in phase 2, and 1,500 patients in phase 3. Using these data parameters, Table 1 shows the representative estimates for COGS on a per-patient basis.

Table 1: Estimates for COGS on a per-patient basis.

Estimates	Phase 1	Phase 2	Phase 3
Annual cost	**$22,685,788**	**$48,828,708**	**$94,798,320**
Personnel cost	$3,610,100	$9,452,298	$20,985,900
Facility cost	$16,666,628	$17,239,032	$18,373,020
Material/supplies cost	$2,160,000	$21,600,000	$54,000,000
Equipment cost	$249,060	$537,378	$1,439,400
Cost per patient	$378,096	$81,381	$63,199

Facility Design Attributes

The impact on facility design attributes on COGS is driven by a number of data elements, as outlined next.

Manufacturing area

As the need for manufacturing capacity increases due to the number of patients that can become part of a defined campaign, the need for increased space to handle increased equipment and operational personnel also increases. Moving from a phase 1 two-patient campaign to increased numbers of patients will require more physical space. If this space is maintained in the same environmental classification for all clinical phases, this will result in an increase in both total installed cost and annual operational costs driven significantly by utilities.

Process utilization

Production costs decrease when the production rate (number of patients) is increased.

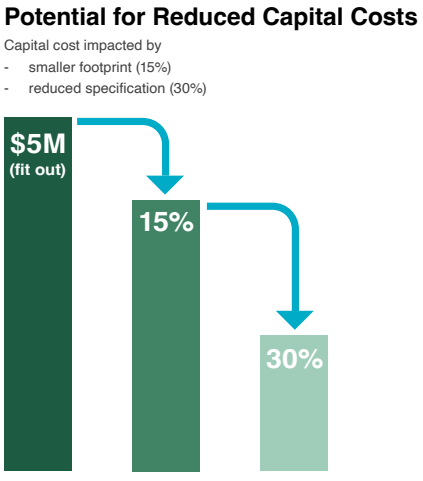
Utilities

Although equipment scale is small, the addition of new BSCs and increases in overall electrical consumption—along with slight increases in water usage—will increase annual utility costs by approximately $1.6 million.

Environmental classification

The ability to implement process closure via equipment design solutions and operational control can have significant impact on annual operational costs. Moving from a Grade A/Grade B environmental product protection solution to a more robust protection solution, such as isolators, can result in reductions in area classifications, decreased environmental monitoring requirements, reduced gowning protocols, reduced cleaning protocols, and reductions in air handler sizing.

Figure 2: Analysis of reduced capital costs.



Process closure

As an example, for the implementation of process closure, a significant amount of work has been done to support the argument that closed system implementation has a significant impact on COGS.

Capital Cost Reductions

BioPhorum developed a case study [6] that identified potential capital cost reductions, a key component of COGS development. The implementation of this particular design attribute produces benefits like energy conservation, reduced facility capital and operating cost, shorter facility construction and qualification times, enhanced facility throughput and operational flexibility, reduced COGS, and speed to market; all while maintaining product quality standards (see Figure 2).

Table 2: COGS breakouts, phases 1 through 3.

Expense	Phase 1	Phase 2	Phase 3
Personnel	$60,168	$15,754	$13,991
Facility	$277,777	$28,732	$12,249
Material and supplies	$36,000	$36,000	$36,000
Equipment	$4,151	$896	$960
Cost per patient	$378,096	$81,381	$63,199

Capital cost reductions have significant impact on COGS. These reductions are defined in the early-phase design efforts.

The single-patient focus of CAR T manufacturing creates scale-up challenges for facility design as patient population increases. In this model, facility size is made up of the actual manufacturing space, laboratory/testing space, office/administrative space, and general assumptions on warehousing and miscellaneous space. The general COGS patient values are established as:

$$COGS/patient = \sum \frac{materials/suppplies + labor + testing + indirects}{\text{annual patients}}$$

It is also important to validate all key model assumptions. These would include patient numbers and how many doses per patient, facility product platform allocation, target throughput per campaign, environmental monitoring sample requirements, qualification costs, automation implementation, baseline total installed costs (TICs) per sq. ft. based on classification, power consumption factors and energy usage intensity, gowning costs per operator, benefit cost, and storage and supply chain.

CONCLUSION

The design decisions made during conceptual design of a manufacturing asset for CTPs have consequential impacts on not only facility capital costs, but also on COGS. "During clinical trials, there is tremendous focus of trial costs as companies reach their phase 3 trials. Decisions made years before in facility design will impact these per-patient values more than many might think. 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/improve market reality. But the facility attributes that impact day-to-day operational costs and manufacturing efficiency, once established, will become baseline, as seen in this COGS model. Speed to market, flexibility and efficiency, and regulatory qualification/compliance are impacted by the decisions about COGS at baseline.

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" [3]. In the following cost breakdown graphics, the cost impacts from personnel, materials and supplies, equipment, and facility attributes are easily seen. The early-phase facility design decisions will have a significant impact on COGS. The details from this model for each clinical phase are presented in Table 2.

Understanding the impact of early-phase design on COGS can support some of the decisions made in equipment selection, area classification designation, segregation strategy, sampling methodology, and operational strategy. These should not be random decisions focused on past approaches. For organizations developing early-stage clinical manufacturing assets for CTP, these decisions will have significant impact on future business models as products enter late-stage development and commercial launch. Optimizing costs early is the goal.

Acknowledgment

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References

1. International Society for Pharmaceutical Engineering. *ISPE Guide: Advanced Therapy Medicinal Products (ATMPs) – Autologous Cell Therapy Products*. Section 4.2.1. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2021.
2. Dream, R., and J. Odum. "Impact of ATMP Manufacturing on Process Equipment and Facility Design." *BioPharm International* 31, no. 11 (1 November 2018):30–34. www.biopharminternational.com/view/impact-atmp-manufacturing-process-equipment-and-facility-design
3. Odum, J. "Engineering Angles: Optimizing COGs in Cell Therapy Manufacturing." *Pharma Manufacturing*. 8 December 2022. www.pharmamanufacturing.com/facilities/article/21437787/optimizing-cogs-in-cell-therapy-manufacturing
4. Meurer, E. "Cutting Costs for Cutting Edge Therapeutic Products: ATMP Process Optimization." *Biopharma Excellence Insights*. 4 December 2018. www.biopharma-excellence.com/2018-12-4-cutting-costs-for-cutting-edge-therapeutic-products-atmp-process-optimization/
5. Mahal, H., H. Branton, and S. S. Farid. "End-to-End Continuous Bioprocessing: Impact on Facility Design, Cost of Goods, and Cost of Development for Monoclonal Antibodies." *Biotechnology and Bioengineering* 118, no. 9 (1 April 2021). https://onlinelibrary.wiley.com/doi/10.1002/bit.27774
6. BioPhorum. "Closed Systems: Data Driven Equipment and Facility Design Case Study." BioPhorum. May 2020. www.biophorum.com/download/data-driven-equipment-and-facility-design-case-study/

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Jeffrey Odum is a recognized expert in biopharmaceutical manufacturing assets. He has authored over 60 published articles and four industry reference books on subjects related to project management, GMP compliance, process improvement, and the design and construction of biopharmaceutical manufacturing facilities. Jeffrey is a Certified Pharmaceutical Industry Professional (CPIP), has served as the ISPE North American Education Advisor, is the past Chair of the ISPE Global Biotechnology Community of Practice, and was Team Lead for the recently published *ISPE Guide: Advanced Therapy Medicinal Products (ATMPs) Autologous Cell Therapy* and the upcoming *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities, Third Edition.* He is a member of the ISPE technical training faculty and is a teaching fellow in North Carolina State University's Biomanufacturing Training and Education Center (BTEC) graduate program in biomanufacturing. He has been an ISPE member since 1994.

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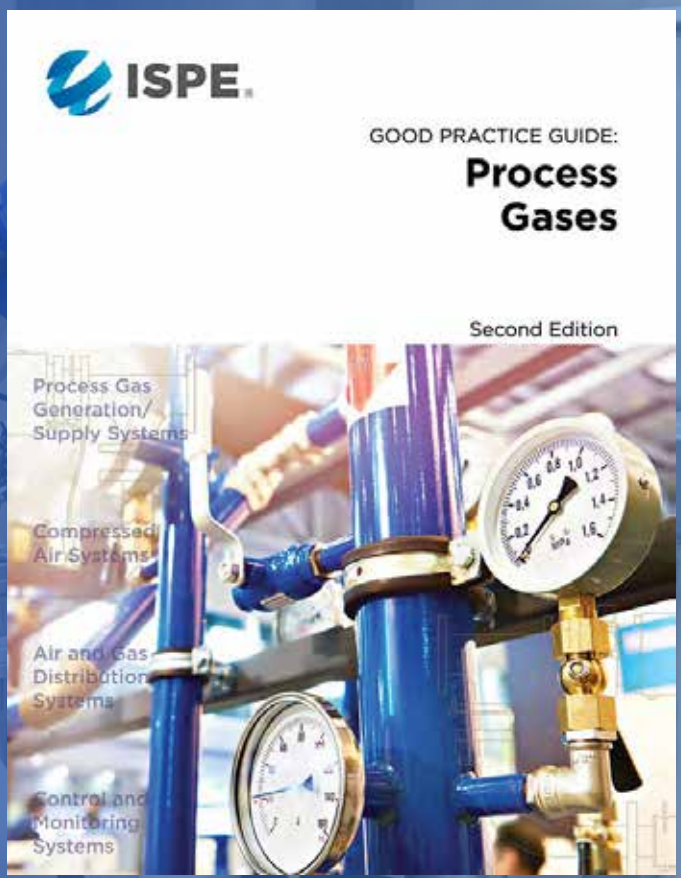

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COMPARABILITY CONSIDERATIONS for Cellular and Gene Therapy Products

By Kathleen Francissen, PhD, Andrew Chang, PhD, Katherine A. Donigan, PhD, Emily C. Hernández, PhD, and Sam Gunter

Cell and gene therapy (C&GT) products comprise a rapidly growing field of innovative medicines that hold the promise to treat and, in some cases, cure diseases that are otherwise untreatable. In this article, we provide points to consider when evaluating the comparability of C&GT when changes are made in their manufacturing processes.

C&GT products—also known as advanced therapy medicinal products (ATMPs) [1]—can present developers with novel circumstances that create technical barriers or otherwise impact their approach to assessing comparability. These products fall under the regulatory framework of biologicals and include a wide array of medicinal products such as gene therapies (both in vivo and ex vivo gene therapies, gene editing technologies, etc.), somatic cell therapies, and tissue-based products. The scope of this article encompasses all C&GT modalities at a high level.

ASSESSING COMPARABILITY

Because C&GT products encompass a broad range of modalities with widely different properties, there is no single broadly applicable approach to assessing their comparability; instead, more tailored fit-for-purpose approaches are needed. For example, many C&GT products are made in limited quantities (by necessity) and there may not be sufficient drug product to evaluate in the usual manner [2, 3].

Comparability assessments are crucial for life cycle management of all biological products, including C&GT, and are used to ensure that manufacturing changes will not have an adverse effect on product quality, safety, or efficacy. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5E guideline [4] provides sound principles for assessing comparability and has been implemented for many years for biotechnological and biological products (e.g., monoclonal antibody products).

The same principles should be leveraged for C&GT products using a risk-based approach, with the appropriate flexibility to account for the extenuating circumstances often posed by these innovative therapeutics. Flexibility is needed to maintain the high standards of C&GT quality and, in some situations, the usual data packages and/or practices for demonstrating comparability of pre- and post-change product may not be suitable.

Manufacturing changes are inevitable throughout the life cycle of a medicinal product and are necessary to ensure continuity of supply and enable best practices for biopharmaceuticals (such as dual sourcing of raw materials). It is generally necessary to scale up or scale out the manufacturing process or introduce new manufacturing facilities to produce enough C&GT product to treat all patients.

Manufacturing processes for C&GT are often complex, but improvements and innovation should be encouraged. In addition, C&GT production can involve several biologically active input materials and, because of their intrinsic variability (from different vendors or batch to batch), focusing a comparability exercise on a particular stage of manufacturing or incoming material can be appropriate. When manufacturing changes are made, the risks associated with the changes should always be assessed and their potential impact on subsequent process steps should be evaluated.

Comparability assessments are needed throughout the life cycle of a medicinal product, from preclinical through commercialization to postapproval [2–7]. During early development,

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For C&GT products, the understanding of their mechanisms of action, manufacturing processes, and product quality attributes is evolving.

comparability exercises generally focus on safety, and in late development focus more on efficacy. However, clinical development of C&GT products is often compressed and may lack the usual distinctions between early and late stages of development.

For C&GT products, the understanding of their mechanisms of action, manufacturing processes, and product quality attributes is evolving. Techniques that enable detection and measurement of product quality attributes may include methods that are more commonly used in research settings and thus need to be adapted to the development environment, and to quality control settings for release assays. Given the current level of understanding of many C&GT products and the inherent complexity of the products themselves, evaluating the impact of manufacturing changes is often a complicated endeavor and may involve multidisciplinary studies, such as in vivo assessments in nonclinical and/or clinical studies [2, 3, 8] more often than for conventional biologics.

Overall, it's important to remember that a comparability exercise is based on scientific principles and does not simply follow a checklist. All available knowledge about the manufacturing process and the medicinal product should be leveraged appropriately. The potential impact and risk of any manufacturing process change should be thoughtfully considered. There is no "one size fits all" approach to assessing comparability of all C&GT given the wide diversity of these products. Regulatory requirements are also evolving, and manufacturing changes may be needed to keep pace with these evolving expectations.

GENERAL PRINCIPLES AND CHALLENGES FOR C&GT

The guideline ICH Q5E "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" [4] sets the regulatory expectations. Developers should evaluate the relevant product quality attributes to show that any changes that would adversely impact the safety and efficacy of the drug product did not occur. The evaluation for conventional biologicals is typically done using a stepwise approach that starts with physicochemical and biological properties of the product to indicate whether nonclinical and/or clinical studies would be appropriate.

The developer's comparability study plans should include lists of predefined manufacturing process changes, analytical methods to be performed, and product quality attributes to be monitored (with well-defined target ranges). The testing plan should include release tests, in-process controls (IPC), stability data, and extended characterization studies. To conduct a meaningful comparability assessment, well-controlled, sensitive, and quantitative assays are needed. Acceptance criteria should be derived by statistical analysis of historical data when it will be meaningful. For C&GT products, tailored approaches are needed.

As described in ICH Q5E, the developer should consider the risk posed by each manufacturing change, including the extent of the change, the particular step in the manufacturing process, and the potential impact to downstream manufacturing steps. When multiple manufacturing changes are to be implemented, a plan should be developed to evaluate the changes stepwise (if appropriate) and/or end to end. The developer must also assess the ability to detect changes in product quality given the status of their analytical methods.

Comprehensive comparability assessments are expected in late-stage development and postapproval, and manufacturing changes should be avoided, when possible, during pivotal trials. In addition, the principles described in ICH Q12 [9] for established conditions and postapproval change management protocols are applicable for postapproval life cycle management of C&GT products.

Challenges arise for C&GT products when there is wide variability in an assay (e.g., infectivity assays for viral-vector-based gene therapies) or wide inherent variability in the final drug product (e.g., autologous cell-based gene therapies or tissue-based products). This can make it difficult to compare drug product batches that have been analyzed in separate analytical test sessions or to set acceptance criteria statistically. Side-by-side testing of pre- and post-change C&GT product in the same test session may mitigate assay variability, though the availability of the product may be limited and/or the shelf life of the product may be short (e.g., 72 hours for tissue-based or cellular products that cannot be cryopreserved).

The analytical techniques for release and stability testing and extended characterization of C&GT should be established as early in development as possible with a strong emphasis on meaningful potency assays. It is not unusual to use a matrix of potency assays to address various aspects of the C&GT mechanism of action. Developers need to carefully introduce new analytical methods in a well-controlled manner and conduct proper method bridging studies to ensure continuity with earlier results.

Comparability guidelines [2–5] also call for process improvements that are not expected to adversely affect product quality, so this leaves room for improved product quality (e.g., lower levels of product- or process-related impurities). When significant benefits, including potential safety benefits, would result from manufacturing changes, such changes should be properly enabled.

When conducting a comparability exercise, an adequate number of representative batches should be included. Although GMP batches are produced to supply clinical trials and the market, non-GMP batches (e.g., engineering runs) may be suitable if they are representative of the process being evaluated. Variability in manufacturing processes should be considered, and the more variability, then the more batches that are needed. It can be challenging to identify and manage sources of variability in C&GT production given the complexity of these medicinal products, their manufacturing processes and testing methods, and the incoming materials used in their production.

POINTS TO CONSIDER

Although there is a need for regulatory flexibility, this should not imply that quality standards can be lower for C&GT products, but rather that alternative approaches may be needed to ensure appropriate standards. Comparability assessments can be particularly important for C&GT products, given that many of these are one-time treatments and the opportunity to re-dose patients is currently limited. C&GT products pose many new challenges and uncertainties, but they also bring new concepts and opportunities. Considerations are herein provided for assessing the comparability of pre- and post-change C&GT products.

C&GT Product Characterization

C&GT products can be complex, and characterization at a molecular level may be achievable for some modalities (e.g., messenger RNA therapeutics) but may be impractical for others (e.g., tissue-based therapeutics). There has been considerable progress in the characterization of viral-vector-based gene therapies. Briefly reflecting on cellular products, these are "living drugs" that are dynamic; their therapeutic effect may be linked to numerous different structures and they may undergo additional changes, such as cell division or migration or engraftment, upon administration to the patient.

For genetically modified cells, extensive characterization is expected, including the off-target and the intended on-target gene editing events. For each genetic modification, analytical tools are needed to assess the expression level, the distribution of expression, and the function for each component. These should be considered when assessing comparability of cell-based gene therapies.

With the emergence of individualized cellular and gene therapies (i.e., products that are custom made for a specific patient where the manufacturing begins with the patient's cells or tissue, like autologous CAR-T cell products and individualized neoantigen-specific immunotherapies), it is not possible to generate reference material of the same composition as the respective individualized product, but analytical standards can be established to ensure method performance.

It's necessary to account for the intended variability of individualized products during comparability assessments. Each batch is highly influenced by patient material characteristics. The patient-specific product quality attributes vary with the corresponding patient and should not be the focus of a comparability assessment. Instead, the product-specific quality attributes should be comparable after manufacturing changes.

These are just a few examples of the complexity presented by these innovative therapeutics. Given their product complexity, C&GT products need to be defined early by the developer. The use of a draft quality target product profile (QTPP) by the developer is encouraged to establish and maintain boundaries for their product as they develop the manufacturing process along with the analytical methods for characterization, release, and stability testing.

Having such a QTPP document in place early in development (for example, a draft during phase I) will help raise awareness of the boundaries of the defined product (and when they may have been exceeded and the developer may possibly have a new product). Potential critical quality attributes (CQAs) should be flagged early, as they will be the focus of the comparability assessment. Because the ability to detect and quantify product quality attributes is often limited for C&GT, there can be limited understanding of the impact of manufacturing changes on product quality, safety, efficacy, and duration of response, and the changes may be challenging to justify in some cases.

Analytical Methods

Analytical methods for characterization, release, and stability testing tend to evolve in parallel with manufacturing process development. With new methods/techniques, product quality attributes that can be detected and quantified often change over the course of development. The comparability assessment should be focused on the most relevant quality attributes of the product and not simply on which attributes can be measured.

Understanding of product quality attributes and the maturity of analytical methods should increase throughout the product development life cycle, so advance planning to reserve appropriate amounts of product for later evaluation is recommended, with the caveat that sample stability over time needs to be kept in mind. Analytical methods for C&GT products are often product-specific, non-compendial, and complex. Early implementation of reference materials and/or assay controls is recommended to enable bridging to new and improved analytical assays.

Potency assays are a pillar of comparability assessments because they measure the bioactivity of the product. Potency measurements are generally challenging for C&GT products because of their complex mechanisms of action, and multiple orthogonal methods are often needed to measure relevant aspects of the product's biological activity. For cellular products, the cells may continue to divide while they are being prepared for and during potency analysis, so there can be inherent variability in these bioactivity measurements.

Product Amounts Available

It is common for C&GT products to be manufactured in limited amounts because of manufacturing constraints or limited amounts of cellular starting material. For example, there are

The C&GT field holds the potential of better correlations of chemistry, manufacturing, and controls (CMC) and clinical data if or when appropriate data and analytics ecosystems are established.

limited amounts of patient cells available for the manufacture of autologous CAR-T cell products. Therefore, the analytical approach taken must accommodate the product and patient needs. There are often only small amounts of material available to develop analytical techniques and to conduct routine analyses and characterization studies, including comparison of pre- and post-change product. For certain compendial assays (e.g., microbiological), there may not be sufficient material available to both treat the patient and conduct a compendial assay, in which case non-compendial methods are required.

Given the small volumes of C&GT production, developers should carefully consider whether it's possible to collect sufficient sample volumes for meaningful analysis and, if so, establish sample retention best practices from early on so that they have retain samples for comparability exercises later in development. It is often not possible to follow standard guidelines on the number of retain samples to keep, especially for individualized products. However, it may be possible to utilize otherwise unused clinical material that was not administered to patients (e.g., for autologous cell-based products).

Assay variability may be inherent in some cases but must be minimized. One approach to overcoming assay variability is to conduct side-by-side analyses with all samples tested in the same analytical run. However, side-by-side analyses may not always be feasible, so the use of established assays with understanding of intermediate precision may be used as a means of analytical comparability testing.

Manufacturing Technologies and Materials

Manufacturing technologies for the production of C&GT are often rather innovative or have transitioned from research settings to GMP manufacturing in recent years. The requirements for pharmaceutical production are much more rigorous than for research, and they require demonstration of process reproducibility, which is important for maintaining continuity throughout clinical development and commercial supply.

In addition, many C&GT manufacturing processes involve multiple biologically active and sourced materials. The purity of incoming materials (raw materials, starting materials, etc.) needs to be verified and documented, and their impact on manufacturing process performance and final product quality and safety need to be evaluated. The designation of incoming materials and the expectations for their quality are areas where additional regulatory guidance and harmonization is being recognized by regulators globally [10].

Many of the incoming materials used for C&GT manufacturing are produced by vendors with limited experience in biopharmaceutical production. Because they may be unfamiliar with medicinal product manufacturing requirements—such as the need to minimize the use of animal-derived materials or the need to minimize the risk of infectious agents, including transmissible spongiform encephalopathy (TSE)—vendors may need guidance from the developer.

In general, the sourcing of raw materials should be done methodically, accounting for the potential impact of raw material quality or changes in their production processes on C&GT manufacturing and product quality. The developer should consider their ability to detect differences in the incoming materials themselves and they may need to conduct their own characterization studies on incoming materials. The ability or robustness of the C&GT manufacturing process to accommodate incoming material variability or changes should also be evaluated. It can be helpful to focus on the most relevant manufacturing steps where the change can be evaluated.

For autologous cell-based products, there is variability in the cellular starting material derived from patients that depends on the disease state of each patient, comorbidities, prior treatments, and other factors. Therefore, the use of surrogate material (i.e., healthy donor cells) should be considered for comparability studies. Nonetheless, material from healthy donors is also heterogeneous, and their representativeness of material from patients needs to be justified. The developer also needs to consider the ability of the C&GT manufacturing process to perform as it is designed to perform in the presence of the surrogate material. Overall, the use of suitable surrogate material allows for better assessment of process-related variability that can be controlled but doesn't address product-related variability.

Split manufacturing

There are several circumstances in which split manufacturing can be an effective approach for assessing comparability of C&GT. For example, when introducing new vendors of raw materials or when conducting a manufacturing site transfer for an individualized C&GT product. The manufacturing stream is split at the point of the change (e.g., starting material) and run downstream. Then head-to-head comparisons can be conducted on, say, the resulting pairs of drug substance or drug product batches, and would generally involve the usual evaluations of release testing and extended characterization.

Split manufacturing requires that there is enough material to

conduct two runs of the process in parallel. This may be possible with, for example, allogeneic cellular products, but may not be feasible with autologous cellular products because patient-derived material is limited in availability. In this case, alternative approaches may be preferable when a risk assessment is supportive, such as the transfer of a fully closed, automated manufacturing process to new sites of manufacture.

Manufacturing process comparisons

Given the inherent complexity and heterogeneity of cellular and tissue-based products, and the associated limitations in their characterization, a comparability assessment may need to focus on the manufacturing process, including IPC and the evaluation of process performance metrics. The manufacturing processes can involve multiple stages, such as expansion of cells, differentiation into a defined mature cell type, or enrichment steps to increase the population of the desirable cell type.

IPCs can provide valuable information about the robustness of the manufacturing process to accommodate modifications in manipulation of the cells. Analytical techniques to better define cellular phenotypes, subpopulations of cells, and cellular impurities are needed. Many of the assays show variability given the dynamic nature of the cells while they are being prepared for and undergoing analysis.

Considerations for Nonclinical Studies

When differences in product quality are detected during the analytical testing, nonclinical studies may be appropriate to assess the impact of manufacturing changes on product quality, safety, and efficacy. This will depend on the type of changes and extent of differences detected between the pre- and post- change product (e.g., product-related substances, process-related impurity profile). For example, new process-related impurities could warrant toxicological studies for qualification through additional nonclinical studies.

Nonclinical studies may provide supplemental information when the available analytical methods for assessing comparability are limited or the level of knowledge of the product is limited. For viral-vector-based gene therapies, this may include comparability of expression/functional assessments in animal models. However, for cellular and tissue-engineered products, there may be few or no meaningful animal models.

Considerations for Clinical Studies

Escalation of comparability assessments may call for clinical studies, though the strengths and limitations should be recognized. It is challenging to develop an understanding of the correlation and/or causation between product quality attributes and clinical outcomes for all medicinal products, and the C&GT field is rather early in developing this knowledge. When clinical bridging studies are performed to further assess comparability, they may provide information on safety and pharmacokinetics, but may not be able to address questions about the possible impact to clinical outcomes, including efficacy and duration of response.

Further, clinical comparability assessments may not be feasible or appropriate in all cases, such as for slowly progressing rare diseases where clinical effects could take years to be observed. When clinical bridging data are needed to evaluate comparability of pre-change and post-change product, there are longer timelines to the initiation of pivotal trials or approval of market applications.

Although C&GT products pose many challenges, they also pose opportunities. Because they tend to be manufactured in small batches for few patients (and even one batch for a specific patient for individualized products), clinical outcomes are more readily traceable on a per-batch basis than for conventional biological products (where one batch can be sufficient to treat thousands of patients). Thus, the C&GT field holds the potential of better correlations of chemistry, manufacturing, and controls (CMC) and clinical data if or when appropriate data and analytics ecosystems are established. It is therefore recommended to archive potentially relevant manufacturing and product quality data as well as clinical data in a searchable and retrievable manner.

CONCLUSION

Typically, comparability exercises are conducted to confirm the established safety and efficacy profile of a biologic product after

incremental manufacturing changes have been made by the manufacturer, leveraging an extensive process and product history linked to clinical experience. With cellular and gene therapies, there is often limited process and product history and depth of understanding.

Although C&GT products have been studied for decades, relatively few products are commercially available, though the number is growing. Certain C&GT modalities are reaching a level of maturity where more detailed expectations for comparability assessments could be articulated in technical guidelines (e.g., viral vector-based gene therapies; genetically modified T cell products).

For C&GT products overall, the manufacturing technologies are often expensive, immature, and rapidly changing. Thus, once the initial feasibility of the medicinal product is demonstrated and supply increases become necessary, switching to state-of-the-art or scalable technologies is required to ensure the best product quality at an affordable cost.

The needed manufacturing changes can result in differences in product quality such that the post-change product may have an equivalent efficacy and comparable or improved safety but does not fulfill the usual expectations of an analytical comparability assessment as currently described in ICH Q5E. This suggests that ICH Q5E does not sufficiently account for the complexity of C&GT product and manufacturing knowledge. An addendum to ICH Q5E could address the novel circumstances faced when assessing the comparability of certain C&GT product modalities when changes are made in their manufacturing processes. In the meantime, developers should obtain feedback from regulators on their comparability study plans to ensure alignment on the approach.

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References

1. European Medicines Agency. Committee for Advanced Therapies. "Reflection Paper on Classification of Advanced Therapy Medicinal Products. EMA/CAT/600280/2010 rev. 1." May 2015. www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf
2. US Food and Drug Administration. "Draft Guidance for Industry. Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products." July 2023. www.fda.gov/media/170198/download
3. European Medicines Agency. Committee for Advanced Therapies. "Questions and Answers: Comparability Considerations for Advanced Therapy Medicinal Products (ATMP). EMA/CAT/499821/2019." December 2019. www.ema.europa.eu/en/documents/other/questions-answers-comparability-considerations-advanced-therapy-medicinal-products-atmp_en.pdf
4. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process." Published June 2005. https://database.ich.org/sites/default/files/Q5E%20Guideline.pdf
5. US Food and Drug Administration. "Guidance Document: Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products." April 1996. www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstration-comparability-human-biological-products-including-therapeutic-biotechnology-derived
6. European Medicines Agency. Committee For Human Medicinal Products. "Guideline on Comparability of Biotechnology-Derived Medicinal Products After a Change in the Manufacturing Process: Non-Clinical and Clinical Issues." July 2007. www.ema.europa.eu/en/documents/scientific-guideline/guideline-comparability-biotechnology-derived-medicinal-products-after-change-manufacturing-process_en.pdf
7. US Food and Drug Administration. "Guidance for Industry. Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information." April 2016. www.fda.gov/files/drugs/published/Comparability-Protocols-for-Human-Drugs-and-Biologics--Chemistry--Manufacturing--and-Controls-Information-Guidance-for-Industry.pdf
8. US Food and Drug Administration. "Draft Guidance for Industry. Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products." March 2022. www.fda.gov/media/156896/download
9. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management." Published November 2019. https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf
10. International Pharmaceutical Regulators Programme. "General Considerations for Raw Materials Used in the Manufacture of Human Cell and Gene Therapy Products. IPRP Reflection Paper." February 2023. https://admin.iprp.global/sites/default/files/2023-03/IPRP_CTWG-GTWG_RawMaterialsReflectionPaper_2023_0215_0.pdf

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LIVE BIOTHERAPEUTIC PRODUCTS: Moving the Microbiome to the Patient

By Emily Heffernan, PE, and Jongmin Paek

Live biotherapeutic products (LBPs) have the potential to treat a wide range of ailments. However, these living microorganisms are difficult to produce due to evolving government regulations and limited GMP manufacturing experience. New facility designs and more specific process guidance could help overcome these challenges. This article explores the nuances of facility design and regulatory requirements for the development of LBPs.

The human microbiome is composed of a diverse community of microorganisms that varies by person based on both genetic and environmental factors. As evidence emerges linking the human microbiome to health and disease, interest in LBPs has followed. These products have the potential to treat a wide range of ailments from cancer to autoimmune conditions.

The US FDA regulatory framework defines LBPs as biological products that contain live organisms (bacteria or yeast) that are intended for the treatment or prevention of disease [1]. One or multiple microbial strains or genetically engineered microorganisms can be used for the production of live cells in LBPs. As defined by the FDA, LBPs exclude vaccines, filterable viruses, oncolytic viruses, and products intended as gene therapy agents.

LBPs are living products and complex to produce. The typical manufacturing process involves fermentation starting from carefully selected cell banks, separation, formulation, and filling followed by lyophilization. Facility design can involve spore-forming organisms, which can require additional containment and biosafety considerations over standard biologics facilities.

MICROBIOME MARKET

In November 2022, the FDA approved the first microbiota-based LBP, and the Australian health authority, Therapeutic Goods Administration (TGA), allowed the debut of microbiome-based therapy. These products are approved for the treatment of recurrent *C. difficile* infections, a condition that causes on the order of 30,000 deaths each year in the United States alone [2]. The Centers for Disease Control and Prevention (CDC) classified *C. difficile* as a top microbial threat to human health in their report, "Antibiotic Resistance Threats in the United States, 2019" [3]. Many other products are in research and development and in various clinical phases. Given this trend, approval and commercial manufacturing of LBPs are imminent.

Although access to microbiome products is limited, with few products at this stage, scientific research on the microbiome continues to highlight new findings and will pave the way for more development and advancement. Microbiome treatments are not limited to infectious diseases. The applications being investigated are varied and range from autoimmune conditions and inflammatory diseases to immuno-oncology applications. Figure 1 provides some data on the range of products in various phases of research and clinical trials as well as intended applications for prospective therapeutics.

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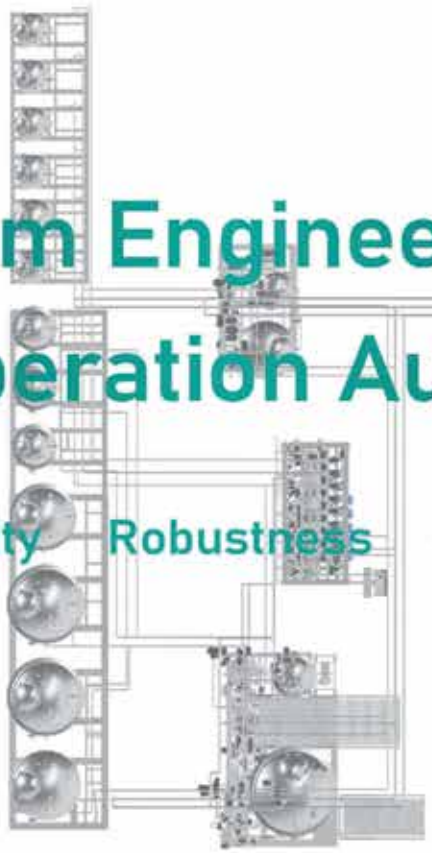

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Figure 1: Clinical trials data for LBPs.

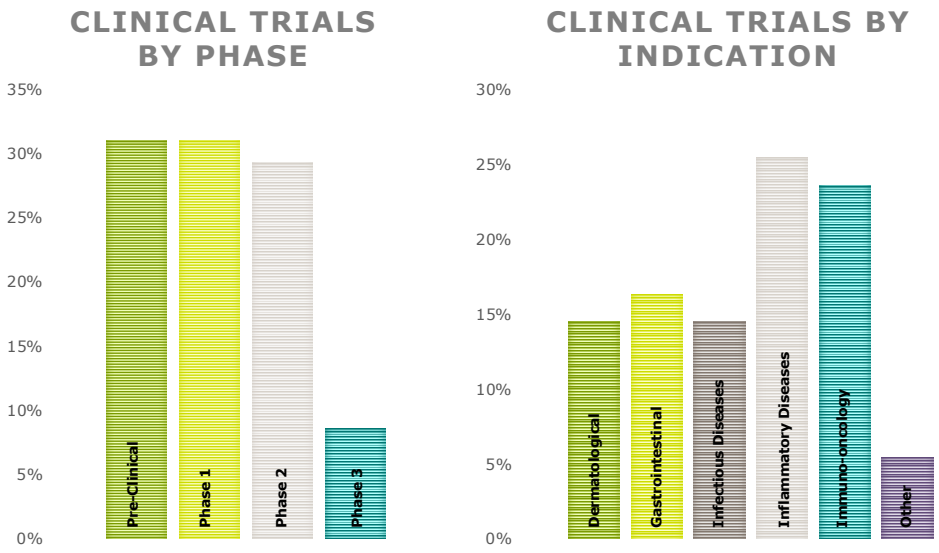
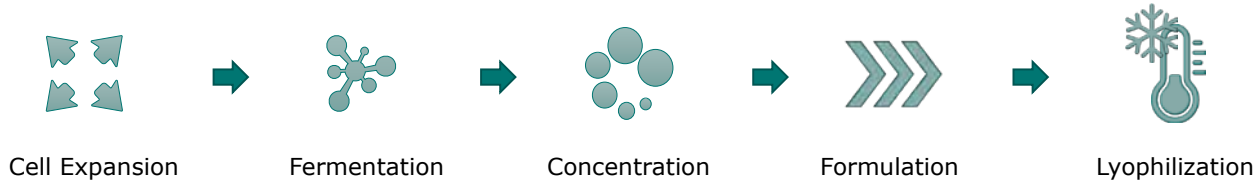


Figure 2: Representative manufacturing platform for LBPs.



LBP MANUFACTURING AND EQUIPMENT CONSIDERATIONS

Microorganism selection begins with each developer identifying strains that deliver a desired beneficial effect to target a specific disease. LBPs may be composed of a single strain; however, multiple strains, also called a consortium, are necessary for some products for proper therapeutic effect. Although a consortium may provide optimal therapeutic benefit, it entails additional manufacturing challenges because growth of up to 50 unique strains may be required for a single product.

Although the fundamental approach of LBP manufacturing processes is not different from other biopharmaceutical therapies, it is important that the manufacturing process is defined with extensive expertise to achieve critical attributes relating to identity, strength, quality, purity, and potency of selected or engineered bacterial strains for target therapeutic effect.

At a high level, microorganisms for manufacturing LBPs can be classified according to their control requirements for molecular oxygen. Traditional biologics manufacturing has focused on the production of aerobic organisms and cannot accommodate the production of anaerobes. Due to the dominance of obligate anaerobic bacteria in the human gut microbiome, along with better stability and viability, many LBP developers choose either facultative anaerobes or strict anaerobes to develop and manufacture LBPs.

Facultative anaerobes can grow in the presence or absence of oxygen, and obligate anaerobes can only grow in the absence of oxygen, a major consideration for production control. The pillars of microbiome manufacturing platform are similar to a typical biological manufacturing process with fermentation, separation, and lyophilization steps. Figure 2 illustrates a representative manufacturing platform for LBPs.

Defining a scalable manufacturing process is a challenge for LBPs because they are novel medicines with limited GMP manufacturing experience. Compliance with an evolving regulatory framework is another hurdle to overcome.

The production process for LBPs begins with preparation of target frozen cells from the working cell bank. Inoculation takes place within an enclosed system depending on the type of strain and sensitivity to environment. Seed fermentation for cell

expansion continues until the target density is achieved and it is transferred to a production fermentor. This is crucial for a scalable biological manufacturing process.

Typical production microbial fermentor sizes range from 500 L to 5,000 L in volume. Both single-use and stainless steel options exist for fermentation. Technology platform selection depends on several factors. Initial setup has differences between single-use and stainless steel, but there is high similarity in the basic method of operation, capabilities, and features.

Stainless steel fermentors are often preferred because they can grow cells to a greater cell density due to their ability to optimize oxygen mass transfer and remove excess metabolic heat. Stainless steel fermentors are also an ideal choice when product dosage and patient population necessitate larger volume production because they offer options that scale up to 5,000 L. Other stainless steel technology benefits include increased resilience to supply chain fluctuations and lower operating costs.

Single-use fermentors are another viable option and can be preferred when the intended patient population or dosage is lower, making smaller-scale production runs a viable option. Single-use fermentors range from 50 L to 300 L, which may require multiple production fermentors operating in parallel if larger volumes are required. The inherent benefits of single-use technology include robust contamination control, operational flexibility, reduced changeover, and reduced process downtime. The elimination of complicated clean-in-place (CIP) and steam-in-place (SIP) cycles and cleaning validation are also favorable.

Downstream concentration is designed in consideration of the fermented microbial broth and the target biomass that unit operations can accommodate to deliver efficient biomass processing either in a batch or continuous setup. The concentration of the cell broth varies depending on the production method and the type of cell strains; therefore, the optimal selection of concentration processing equipment is critical to retain the target cell solid in a reproducible manner.

After fermentation and concentration, the product is formulated with sterile buffers and cryopreservatives. At the conclusion of formulation, the product is lyophilized. Lyophilization is conducted to dehydrate the live biotherapeutic substance and gain stability in the final substance. Filling and lyophilizer loading must take place within a Grade A (ISO 5) designed environment with appropriate containment to avoid contamination of the product or surrounding space. The use of barrier isolator technology may be employed for contamination control and containment and to maintain a reduced oxygen environment if necessary for the product.

After lyophilization, the product is transferred to an intermediate bulk container (IBC). Milling of the product may be required to achieve a specific particle size range and is followed by a blending process. Additional excipient materials are added, and the IBC is rotated to mix the powder. After blending, the IBC is transferred to an encapsulation machine. Although LBPs are researched and developed in various forms, current trends show that capsules are the dominant form within the microbiome space. Oral delivery of LBPs should endure acidic conditions and prevent release of the drug product until it reaches the target intestine. Securing enteric protection is also a critical element for process and product development.

The encapsulation process involves transferring the product into a machine that precisely doses the blended product into gelatin capsules. The machine places a gelatin cap and closes the capsule. Encapsulation systems can include integrated check weighing and metal detection. Capsules are collected in a bin or tote in preparation for final packaging. Product containment during blending and encapsulation should be designed to avoid contamination of the product and the surrounding room.

MANUFACTURING FACILITY CONSIDERATIONS

The manufacture of LBPs necessitates distinctive facility design considerations to account for enhanced biosafety levels, manufacture of spore-forming organisms, and multi-strain production.

Spore-Forming Organisms

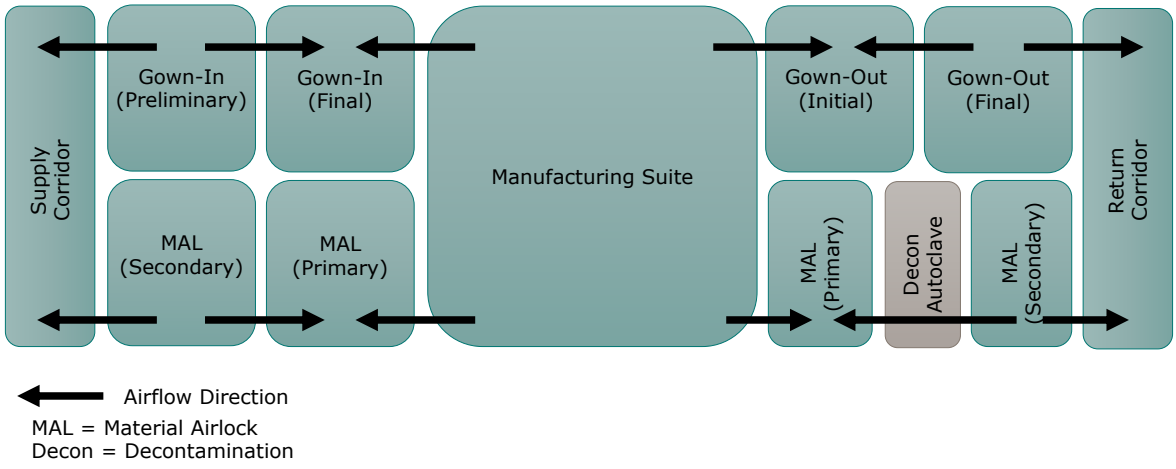
Spore-forming microorganisms are preferred or chosen for product research and development due to the ability of spores to survive passage through the acidic conditions of the gastrointestinal tract. However, when transitioning to large-scale manufacturing, tough questions must be addressed to control the risk of cross-contamination.

The formation of spores allows for bacteria to survive under adverse environmental conditions, including extreme temperatures, dryness, chemical agents, and even ultraviolet radiation. The *Bacillus* and *Clostridium* species are among the LBPs that are spore formers. Dormant spores can survive for many years; when conditions are favorable, the spores can germinate to an active or vegetative state.

Given the robustness of spore-forming organisms, careful consideration must be given to the facility design for the manufacture of these species. The FDA has published "Guidance for the Industry on Manufacturing Biological Intermediates and Biological Drug Substances Using Spore-Forming Microorganisms" [4]. Although previous regulations mandated that work with spore-forming organisms be performed in a separate building from non-spore-forming organisms, the latest guidance allows for greater manufacturing flexibility. When manufacturing spore-forming organisms in a multiproduct facility, the paramount concern is prevention of cross-contamination due to the persistent nature of spores. This can be accomplished by a combination of physical containment (equipment and facility design) and procedural controls.

Per the regulatory guidance, double airlocks should be employed for incoming personnel, materials, and exiting waste. Figure 3 illustrates the preferred manufacturing suite arrangement: unidirectional flow of personnel and materials with segregated double airlocks for incoming and exiting personnel and materials. The interior airlocks are negatively pressurized to surrounding spaces to enhance containment. Single-pass (100% outside) air is also recommended for spore-forming product spaces.

Figure 3: Preferred production layout for spore-forming organisms.



Equipment should be dedicated if possible and the use of single-use equipment is encouraged. If equipment is used on a campaign basis for both spore-forming and non-spore-forming organisms, it must be decontaminated via a validated changeover procedure between campaigns. Manufacturing suites must also undergo a validated decontamination procedure. Use of a gaseous or vapor-phase sterilant, such as vapor-phase hydrogen peroxide (VPHP) or chlorine dioxide gas (ClO_2), should be considered and will be discussed in further detail.

Recommended procedural controls include multiple stages of gowning and de-gowning of personnel to minimize the risk of spore-forming organisms exiting the production areas. Personnel who work in spore-forming areas are also encouraged to shower prior to working in other areas of the facility.

Biosafety Level Considerations

Biosafety level design considerations are defined in the US by the NIH in "NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules" and by the CDC in "Biosafety in Microbiological and Biomedical Laboratories (BMBL), 6th Edition" [5, 6]. With increasing biosafety levels, greater protective measures are implemented to protect both the operator and the environment from potentially adventitious agents. Most LBPs are classified as biosafety risk group 2 (BSL-2 or BL2) because they are pathogenic or infectious organisms that pose a moderate health hazard. Additionally, per the NIH, most LBP facilities are classified as "large scale" due to working with volumes of greater than 10 L per container.

LBP facilities are often designated as "BSL-2 enhanced," or BSL-2+. Although this is not an officially recognized classification by either the NIH or CDC, it indicates that all the requirements for BSL-2 are implemented, along with select BSL-3 level requirements as an added means of protection.

Vapor-Phase or Gaseous Sterilization

Although not a regulatory requirement, many LBP manufacturers incorporate either portable or integrated gaseous or vapor-phase sterilization into their facility design. There are many commercially available sterilants; however, the most commonly used in spore-forming facilities is vapor-phase hydrogen peroxide (VPHP). Gaseous or vapor-phase sterilants are used to destroy all microorganisms that are potentially contaminating a given space. These sterilants are all oxidizers that work by disrupting the cell membrane or cell walls of microorganisms, which in turn leads to cell lysis and death.

Gaseous or vapor-phase sterilants may be used on a periodic basis for campaign changeover and for emergency decontamination in case of a product spill or breach. There are options to integrate this fumigation system fully into the facility design or to contract out the sterilization on a periodic basis using portable units. When considering use of a gaseous or vaporized sterilant, the materials of construction for the equipment and manufacturing space should be evaluated, including whether HVAC ducting will be included as part of the sterilization process.

Not all materials are compatible with fumigation chemicals commonly used in the pharmaceutical industry, including chlorine dioxide, hydrogen peroxide, and formaldehyde. Sterilization chemical selection should be evaluated with regard to multiple different factors, including the spore-forming organisms that are expected to be manufactured or present in the facility because some sterilants are more effective at destroying certain species than others.

REGULATORY CONSIDERATIONS

As there is continuous effort to improve the clarity on regulatory requirements for microbiome-based products and LBPs, it is imperative that product development should be conducted in good

communication with regulatory authorities. In the US, LBPs are regulated by the FDA through the Center for Biologics Evaluation and Research (CBER). In 2016, the FDA issued a guidance document for early phase clinical trials of LBPs [1].

In the EU, LBPs are considered biological medicinal products and are regulated under guidelines for other biological products such as vaccines. In addition, guidance specific to LBPs has been developed. In 2019, the EU released a monograph addressing LBPs for human use [7].

It is important to note that the guidances issued to date are primarily focused on requirements for clinical trials, with little advice available for commercial drug regulatory requirements due to the developmental nature of LBP manufacturing. For an Investigational New Drug (IND) application, both the FDA and EMA expect specific information and guidance requirements are in place for both drug substance and drug product. The CMC requirements for drug substance products for LBP INDs are (a) the LBP description, including strain designation, source, phenotype, and genotype; (b) the LBP's characterization, including antibiotic resistance profiles; and (c) the method of manufacture, including raw materials, production flow chart, cell banking, cell growth and harvest, purification, and in-process testing. The CMC requirements for drug products for LBP INDs are the composition; manufacturer; specification, including identity, potency, purity, and microbial bioburden; stability; placebo; and environmental assessment.

CONCLUSION

Although there are few commercially approved LBPs to date, the clinical pipeline shows a number of products with promise and a commercially approved product is likely in the near future. The manufacture of LBPs is unique from both an equipment and facility design perspective due to the requirements of facultative and strict anaerobes, spore-forming organisms, and because the end product is a living organism. Biosafety considerations and the implementation of facility controls to maintain containment requirements are crucial. Both the FDA and EMA have issued regulatory guidance, but it primarily focuses on CMC requirements for IND applications, with less focus on how drug regulatory requirements are to be addressed in practice.

References

1. US Food and Drug Administration. "Guidance for Industry. Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information." Updated June 2016.
2. UVA Health. "Revealed: The Secret Superpower That Makes C. Difficile So Deadly." UVA Health Newsroom. 15 April 2019. https://newsroom.uvahealth.com/2019/04/22/revealed-the-secret-superpower-that-makes-c-difficile-so-deadly/
3. Centers for Disease Control and Prevention. Department of Health and Human Services. "Antibiotic Resistance Threats in the United States, 2019." December 2019. www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf
4. US Food and Drug Administration. "Guidance for Industry. Manufacturing Biological Intermediates and Biological Drug Substances Using Spore-Forming Microorganisms." September 2007.
5. National Institutes of Health. Department of Health and Human Services. "NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules." April 2019. https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf
6. Centers for Disease Control and Prevention and National Institutes of Health. *Biosafety in Microbiological and Biomedical Laboratories (BMBL), 6th Edition.* June 2020. www.cdc.gov/labs/pdf/SF__19_308133-A_BMBL6_00-BOOK-WEB-final-3.pdf
7. The European Directorate for the Quality of Medicines & HealthCare – EDQM. "Live Biotherapeutic Products for Human Use 3053 Monograph. *European Pharmacopoeia* 9 (2019):6522–3.

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

Jongmin Paek is the Chief Manufacturing Officer at List Biotherapeutics Inc., specializing in contract development and manufacturing for LBPs. He is leading a new LBP manufacturing site project, overseeing facility and process design, technology innovation, and organizational development in the company. With over 23 years of global experience in biomanufacturing and pharmaceutical fields, Jongmin has developed extensive expertise in biological drug substance, sterile parenteral drug product manufacturing, small molecules, and drug delivery systems. He holds a BS in fine chemical engineering from Chonnam National University, Korea. He joined ISPE in 2022.

CoP
LEADER
PROFILES

ERICH H. BOZENHARDT

Erich H. Bozenhardt is the Associate Director of Process Engineering in Regenerative Medicine Operations at United Therapeutics. Erich is an experienced bioprocess subject matter expert and internationally recognized authority in the areas of cell and gene therapy and bioprocessing. He has published more than 30 technical papers and is a frequent presenter at conferences.

Erich has been a member of ISPE since 2005. He is Chair of the ATMP Community of Practice (CoP) Steering Committee and has volunteered on many ISPE Guidance Documents teams, including those for the *ISPE Guide: Advanced Therapy Medicinal Products (ATMPs) – Autologous Cell Therapy* and the *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities*. He is currently volunteering with teams producing ISPE Guidance Documents on risk-based validation of ATMPs, allogeneic cell therapy, and cell therapy equipment design.

Erich has been with United Therapeutics for three years and is responsible for all phases of manufacturing facility design and construction, implementing manufacturing technologies at GMP scale, and tech transfers. Since its inception, the company has strived to find a cure for pulmonary arterial hypertension and other life-threatening diseases. The company is also working to create an unlimited supply of manufactured organs for transplantation, including through xenotransplantation and 3D organ bio-printing technologies.

"We have multiple programs that are currently at the preclinical stage. This is a space where there is not a lot of industry precedent and I get to cycle between building a strategic framework and tactical execution. For both I'm learning from others and trying to develop new solutions. We're trying to manufacture organs, so this is not something where we can use normal process equipment. I work with our R&D team to understand what they need and then determine how we can bring our technology into GMP manufacturing."

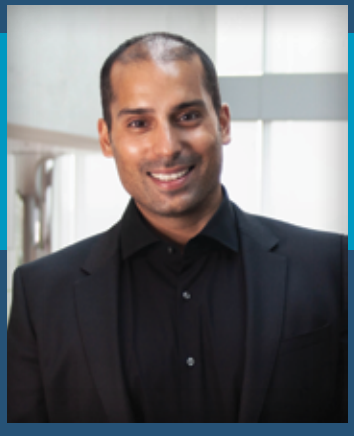
Erich was always interested in biology and building things. He says that pharmaceutical engineering was the perfect field to combine both interests. He knew he had made the right career choice after working on a project developing a CAR T cell therapy for people with relapsed myeloma: a diagnosis that often means the patient will not live for more than six months. "We were able to go lightning fast from project concept to completion. We finished in about 11 months instead of the projected timeline of 16 to 18 months."

"A few months after we finished the project, I was talking to the client, and they told me they had already dosed several patients and had a response rate of greater than 90%. I realized that because we were able to complete the project sooner than anticipated, they were able to treat a whole cohort of patients who otherwise might not be alive. That day I was able to realize the impact that I can have on patients' lives just by being an engineer. It really strengthened my passion, which I carry forward with me into the work that I'm doing with United Therapeutics."

"There are a lot of people developing truly unique solutions for ATMPs, but there's no industry best practice yet. It seems like every couple of months, there's something new coming out—some new variation and the ATMP CoP is a great opportunity to come together to discuss different challenges and solutions."

To join the conversation about ATMPs, visit the Advanced Therapy Medicinal Products Forum on ISPE Engage at cop.ispe.org/forums

— Marcy Sanford, ISPE Publications Coordinator



MICHELANGELO CANZONERI

Michelangelo Canzoneri, PhD, is a seasoned leader in the digital transformation space within the healthcare and life science industry currently serving as the Global Head of Group Smart Manufacturing at Merck KGaA, Darmstadt, Germany. In this pivotal role, he functions as the primary business interface across the life science, healthcare, and electronics sectors, steering the incubation, harmonization, and scaling of smart manufacturing and supply chain analytics capabilities. Collaborating with various business and IT functions, Michelangelo has co-created a unified vision and strategy that encompasses both sector-specific and cross-sectoral domains, guiding the development of comprehensive roadmaps.

Since joining ISPE in 2015, Michelangelo has fostered a rich relationship with the organization. He chairs the ISPE Biotechnology Community of Practice (CoP) and plays a key role in authoring ISPE whitepapers, guidance documents, and other articles. His leadership further extends to advisory roles within the ISPE Germany/Austria/Switzerland (D/A/CH) Affiliate and contributions to ISPE conferences. As a mentor in the ISPE Emerging Leaders program, he promotes knowledge sharing and collaborative growth, a sentiment echoed in his podcast, "The Power of Curiosity and Why It's Important in Your Transformation Journey."

Before his tenure at Merck KGaA, Michelangelo held pivotal roles at Sanofi, starting his career as Laboratory Head in Upstream Process Development. He later assumed the role of Head of Technology and Innovation Therapeutic Proteins. In this capacity, he spearheaded global initiatives and innovation in therapeutic proteins. Michelangelo was instrumental in developing a management and stage gate process to identify, incubate, and scale technology innovation for global biologics, encompassing both CMC and commercial manufacturing spheres. His visionary leadership led to the creation of a knowledge management platform, facilitating the global team at Sanofi to find information and connect with experts worldwide, thereby enhancing the repository of knowledge and expertise pertaining to technologies for the development and manufacturing of biologics.

A staunch advocate for education, Michelangelo imparts knowledge as a professor at the University of Applied Sciences and the Goethe Business School in Frankfurt, Germany, and as a guest lecturer at Massachusetts Institute of Technology (MIT). He nurtures the forthcoming generation of leaders in the industry, emphasizing a culture of curiosity and continuous learning. In this educational capacity, he has supervised numerous Bachelor, Master, and PhD theses, fostering critical thinking and innovation in the next wave of industry professionals.

Beyond his technical expertise, Michelangelo is a certified Myers–Briggs Type Indicator (MBTI) coach, leveraging this certification to foster better understanding and collaboration in change management projects. He offers coaching sessions to help individuals learn more about themselves and others, enhancing team dynamics and personal development.

Michelangelo's career stems from a personal connection, inspired by a desire to assist patients like his father, who battled MS. This early curiosity evolved into a rewarding career, where he feels "privileged to work with passionate and dedicated global teams focused on impacting patients' lives through innovative approaches."

In his advocacy work, Michelangelo highlights the synergistic use of advanced technologies, including process analytical technologies paired with sophisticated data analytics and artificial intelligence.

Michelangelo continues to be a thought leader in the field, with a substantial portfolio of publications and patents. He has notably contributed to book chapters, including one on "Digital Twins: A General Overview of the Biopharma Industry," showcasing his deep understanding and foresight in the digital transformation of the healthcare and life science industry. He remains committed to steering the industry towards a future characterized by manufacturing excellence and transformative solutions.

2023 BIOTECHNOLOGY CONFERENCE: Keynote Presentations

By Scott Fotheringham, PhD

The 2023 ISPE Biotechnology Conference opened on 26 June with a series of six keynote presentations on biotechnology and the development and manufacturing of advanced therapies. Tom Hartman, President and CEO of ISPE, introduced each of the keynote speakers.

KEYNOTE SPEAKERS

The first speaker, Michael Lohan, CEO of the Industrial Development Agency (IDA) of Ireland, stressed the importance of the biotechnology industry to the host country, as well as the value of having access to the European market and regulatory regime for biopharmaceutical and medical device companies in Ireland. In particular, Lohan discussed the ways companies are supported in their push to digitalize and embrace green manufacturing solutions.

Evdokia Korakianiti, Head of Quality and Safety of Medicines at the European Medicines Agency (EMA), spoke about the ways European regulators are supporting manufacturers, specifically via the work of a new group at the EMA. Jim Faulkner, PhD, Venture Partner at Apple Tree Partners, gave an overview of the role venture capital plays in the current success of biologics and what will be needed to bring other innovative therapies in the research and development (R&D) pipeline to market.

Cynthia Pussinen, Chief Executive Officer, Sernova, described what the biotech industry needs to reap the rewards of innovation. Michelangelo Canzoneri, Global Head of Group Smart Manufacturing, Merck KGaA, laid out the strategy the company is using to evolve to smart manufacturing, with tools such as digital twins and modular type packaging. Peter Marks, MD, PhD,Director of the Center for Biologics Evaluation and Research (CBER) at the FDA, rounded out the keynotes with how the lessons learned during the COVID-19 pandemic can be applied to advanced manufacturing, including a communications pilot called Operation Warp Speed for Rare Diseases.

ENABLING BIOTECH INNOVATION AND FUTURE SUCCESS IN IRELAND

Michael Lohan, CEO, Industrial Development Agency of Ireland

Lohan highlighted the importance of life sciences advanced manufacturing to Ireland's economic well-being. The IDA is an agency tasked with attracting and retaining foreign investment in technology, life sciences, and other industries. Its guiding strategy, Driving Recovery and Sustainable Growth, prioritizes investments in R&D, digitalization, talent development, and sustainability [1].

For regulated industries, such as biopharmaceutical and medical device manufacturing, an Irish base provides access to the European regulatory framework and markets, robust R&D, and a skilled workforce to supply the industry with the specialized engineering skills and expertise required to design, build, commission, and validate facilities. Companies providing medical devices, small molecule active pharmaceutical ingredients (APIs), biologics, cell and gene therapies (C&GTs), and life sciences services have made these recent investments:

- AstraZeneca: €400 million in small molecule clinical manufacturing
- Eli Lilly: Increased investment to €1 billion in high-output advanced biologics manufacturing
- Dexcom: Building a medical device manufacturing site
- MSD: Biologics accelerator
- MeiraGTx: Gene therapy manufacturing facility

Digitalization, Green Manufacturing, and Collaboration Are Essential for Future Success

The IDA anticipates a coming wave of C&GT investment, as seen by the presence of manufacturers MeiraGTx, Takeda, and Pfizer. The IDA has invested €21 million to expand the National Institute for Bioprocessing Research and Training, including two new training facilities, to meet the needs of this growing sector [2]. The evolution to Industry 5.0 requires companies to provide training for the workforce and challenges the IDA to help address this with access to technology, instructors, and de-risking investment through

government funding, including the creation of a digital manufacturing center, Digital Manufacturing Ireland [3].

Green manufacturing continues to grow with investments in solar energy by Eli Lilly and MSD, as well as the designation of Janssen Sciences Ireland as part of the World Economic Forum's Global Lighthouse Network.

Partnerships and collaboration will lower the risk of innovation. The Disruptive Technology Innovation Fund, a €500 million fund of the Irish government, has supported projects in many areas, including smart wearables, the use of artificial intelligence (AI) for cancer diagnosis and treatment, remote patient monitoring, and blockchain for medical device cybersecurity [4].

PATIENT ACCESS THROUGH INNOVATION

Evdokia Korakianiti, Head of Quality and Safety of Medicines, EMA

Korakianiti shared the EMA's goals to promote advanced manufacturing, as laid out in its strategic report, EMA Regulatory Science to 2025 [5]: catalyzing the integration of science and technology in drug development (including a focus on digital technologies) and enabling and leveraging research and innovation in regulatory science.

Korakianiti said that realizing the benefits of advanced manufacturing requires a predictable regulatory framework, exchange of information between drug developers and regulators, and regulatory convergence with other regions.

Quality Innovation Group

The Quality Innovation Group (QIG) is a team of EMA inspectors that supports the use of innovations in design, manufacturing, and quality control [6]. The QIG works with academics and medical experts, regulatory agencies from other regions, and industry. Stakeholders can access scientific advice from the QIG, get help with an initial application, and receive input on reviews and inspections. The group's near-term priorities are continuous manufacturing of biologics, decentralized manufacturing, and automation.

Its first focus group, on continuous and decentralized manufacturing, recommended to the European Commission a derogation of the rules for remote sites (e.g., hospitals) that require marketing and importation authorization (MIA), which includes compliance with cGMP and inspections [7]. It also recommended a "regulatory sandbox" to allow the EMA to work with member states and developers to test altered requirements for products that provide great benefits to patients but cannot be developed in compliance with current regulations.

International outreach helps identify mutual priorities, including engagement on common guidance documents and collaborative assessment procedures. The EMA is a member of the International Coalition of Medicines Regulatory Authorities, which launched two pilot programs related to advanced manufacturing [8]:

- The ICMRA Pilot Program for Collaborative Assessment of COVID-19 Related CMC Post-approval Changes, which aims to avoid delays to approval times for postapproval changes [9]
- The ICMRA Pilot Program for Collaborative Hybrid Inspection to reduce travel restrictions and increase inspection capacity [8]

Advanced manufacturing is a key priority of the EMA to improve access, availability, and affordability of medicines to Europeans.

FUTURE BIOTECH PORTFOLIO: CHALLENGES TO TRANSLATE BIOTECH INNOVATION INTO VIABLE THERAPEUTICS

Jim Faulkner, PhD, Venture Partner, Apple Tree Partners

Faulkner shared how venture capital firms are key to the success of companies developing novel drugs in a range of modalities, including gene editing platforms, oncolytic viruses, CAR T cell therapies, RNA therapeutics, and bioelectronics, including medical devices.

Faulkner identified three core themes that are woven throughout multiple modalities:

1. Synthetic biology will continue to be important: This includes advanced therapies that exploit the immune system to fight cancer, alter the transcriptome, or manipulate cell-to-cell communication using tools like exosomes.
2. Complex diseases require sophisticated solutions: The cause of virtually every known disease is multifactorial, so single-point interventions are unlikely to be effective. Yet combining multiple products is problematic. Advanced therapeutics, such as multifunctional molecules, will continue to take on greater importance.
3. Delivery of therapeutics: Immune rejection, systemic side effects, and getting across the blood-brain barrier are challenges that might be overcome through targeted approaches.

Translating innovations requires being willing to throw away current paradigms that don't work and inventing new processes and technology. This has to happen with cost in mind to ensure medicines are accessible to large numbers of patients around the globe. Getting a drug candidate to commercial production requires considering whether there are any single-source materials in the supply chain, the process has been vetted by regulators, and the process is transferable to a different manufacturer as well as the need to minimize the cost of goods and how to address scalability challenges.

Faulkner concluded with three things needed for future success: be ready for, and anticipate, change; ensure a company is prepared to evolve as circumstances change; and have courage to address innovative modalities that will create the most exciting upcoming medicines. Every adventure has a beginning.

REALIZING THE FULL POTENTIAL OF ADVANCED THERAPIES

Cynthia Pussinen, Chief Executive Officer, Sernova

Despite the challenges of advanced therapies manufacturing—failure rates in clinical studies, long timelines, and excessive drug development costs—Pussinen knows these products continue to provide an intellectual challenge and the chance to treat or cure diseases. The landscape for advanced therapies is rapidly evolving.

Among the 24 approved gene therapies, most treat hematologic cancers, though there is hope that some of the more than 2,000 gene therapies in clinical studies will extend to efficacy in solid tumors. In April 2023, Vertex Pharmaceuticals and CRISPR Therapeutics submitted the first CRISPR therapy for FDA approval, an ex vivo cell therapy for sickle cell disease and beta-thalassemia. Noting that the industry is at an inflection point of growth, Pussinen shared what needs to be done to achieve further success [10, 11].

The Challenges of CMC for Advanced Therapies

Preventing lengthy delays for biopharma manufacturing depends on the success in CMC deliverables. Pussinen noted that CMC issues cause more disruptions and delays in C&GTs than in monoclonal antibody development during phase 3 trials, regulatory submission, and especially regulatory review. Particularly vexing are insufficient CMC data packages, comparability/analytical issues, and site-inspection issues.

Pussinen offered advice in 11 areas where improvement is needed to speed the delivery of C&GTs, including:

- "The process is still the product": Enter phase 1 trials with a process as close to what it will be for commercial production as possible. Leverage data with automation and digital twins.
- Analytical development: This needs to be started earlier than for other modalities. A range of assays should be used to understand the product, given lab-to-lab variability, variability of raw materials, and lack of reference standards.
- Manufacturing success: Whether to outsource, insource, or rely on a hybrid approach carries more risk for advanced therapies. Not all contract development and manufacturing organizations (CDMOs) have the experience needed to develop or commercialize a C&GT. The high cost of goods will likely decrease with improved titers and yield, and as the industry continues down the path of digital maturity.
- Talent scarcity: The demand for biomanufacturing talent and leadership is likely to outstrip supply in the near future due to an aging workforce and growth in the sector.

MERCK'S JOURNEY TO SMART MANUFACTURING

Michelangelo Canzoneri, Global Head of Group Smart Manufacturing, Merck KGaA Darmstadt, Germany

Canzoneri pointed out that although 80% of manufacturers operate their facilities at level 2 of the Digital Plant Maturity Model (DPMM), few advanced therapy companies have fully leveraged the promise of Pharma 4.0™ [12]. Challenges abound, including multiple enterprise resource planning (ERP) systems with incompatible technologies, data silos, and the amount of unstructured data that cannot be leveraged without excessive manual work.

Smart manufacturing allows companies to use digital technologies and data analytics to optimize the way advanced therapies are developed, manufactured, quality controlled, and delivered. Canzoneri outlined the strategy and tactics Merck is using to transition to smart manufacturing.

The road to a predictive plant (DPMM level 4) or an adaptive plant (DPMM level 5) starts with expensive foundational change followed by digital transformation and ends with smart manufacturing. Canzoneri shared use cases demonstrating that time to market can be reduced by 83% through digital twin technology and labor productivity can be increased by 90% through the use of advanced analytics.

Antibody Production Digital Twin

There are different maturity levels of a digital twin, from one that virtualizes human–machine interfaces to one that models "lights-off" cognitive manufacturing. Merck's digital twin of a monoclonal antibody (mAb) production process has cut process development time in half while reducing the use of materials and energy. Leveraging data and computational fluid dynamics, Merck is able to predict cell growth and titer. In the future, it hopes to be able to also predict quality attributes of the mAb.

Modular Manufacturing Sites

Plug-and-play modular type packaging (MTP), based on the OPC Foundation's unified architecture (UA) and contextualized with additional data, allows Merck to plug any piece of equipment into its IT infrastructure. There it is recognized and augmented by, for example, a digital twin of the process [13].

These projects are extending Merck's smart manufacturing capabilities. Some are solely internal activities, such as distribution fleet management and track and trace, whereas others involve external partners, like supplier risk and inventory management.

Canzoneri advised companies planning on evolving to smart manufacturing to:

- Assess and prioritize the underlying problems to be addressed
- Identify gaps and the capabilities and technologies needed to address them
- Create a scalable roadmap to be implemented through collaboration among internal teams and external partners

THE IMPORTANCE OF MANUFACTURING IN THE DEVELOPMENT OF ADVANCED THERAPIES

Peter Marks, MD, PhD, Director, Center for Biologics Evaluation and Research, FDA

The rate-limiting step for the deployment of COVID-19 vaccines was neither clinical trials nor regulatory reviews, according to Marks. Instead, it was manufacturing: namely process development and scale-up. Accelerated COVID-19 vaccine development saw parallel-tracked clinical phases, and manufacturing scale-up to millions of doses began as soon as the vaccines showed promise.

Advanced manufacturing could have helped by providing agility, flexibility, reliability, and reproducibility of vaccine manufacturing through continuous, or semi-continuous, processes. It's amenable to process control using real-time analytics and can lead to process improvements. Scaling production is

easily achieved, either with an increase in the size and number of bioreactors or by using continuous manufacturing. The technology can be packaged in portable units, making rapid deployment of production possible anywhere in the world. "Advanced manufacturing offers the potential for improved agility, reliability, and cost reduction for the manufacturing of complex biological products," Marks said.

Marks noted that the incredible promise of C&GT is hampered by manufacturing challenges, lengthy clinical development timelines, and varying regional regulatory requirements. CBER is addressing these challenges by supporting research in advanced manufacturing technologies, using accelerated approvals to reduce the length of clinical development, exploring global regulatory convergence, and initiating a communications pilot, Operation Warp Speed for Rare Diseases. Using the positive experience of frequent communication with sponsors during the pandemic, CBER hopes to use this pilot to accelerate the speed of development of rare-disease gene therapies. If successful, CBER might expand the pilot program to other products.

Automation might improve the commercial viability of gene therapies, which tend to have an exorbitant cost per dose. Companies could apply the closed systems with semi-automatic manufacturing used to make CAR-T cell therapies. The downstream process to produce an adeno-associated virus (AAV) vector for a gene therapy can also be automated, potentially leading to improved consistency—something that doesn't exist now. CBER is also working with partners to develop a gene therapy fabrication device.

CBER, along with the Bespoke Gene Therapy Consortium, is looking for ways to encourage the use of similar methodologies, which should allow more smooth technology transfers from academics to contract manufacturers. There are also changes to legislation that should allow manufacturers to leverage nonclinical data and manufacturing information from an approved product (e.g., a vector backbone with a gene insert) for another product, thus reducing the regulatory burden [14].

CONCLUSION

These insights from government agencies, regulators, investors, and industry underscore how exciting this time is for the production of advanced therapies. There are challenges, but they are surmountable. As Faulkner said, "Every adventure has a beginning, and it takes courage to step out of what you've been doing for many years. It's going to take courage for us as engineers to change what we're doing and address these modalities that are going to create some of the most exciting medicines of the future."

References

1. IDA Ireland. "Driving Recovery and Sustainable Growth 2021-2024." September 2023. www.idaireland.com/driving-recovery-and-sustainable-growth-2021-2024/
2. National Institute for Bioprocessing Research & Training. September 2023. www.nibrt.ie/
3. Digital Manufacturing Ireland. "Transforming Value Chains Through Innovative Technology Adoption." September 2023. www.dmireland.org/
4. Department of Enterprise, Trade and Employment. "Disruptive Technologies Innovation Fund." September 2023. https://enterprise.gov.ie/en/what-we-do/innovation-research-development/disruptive-technologies-innovation-fund/
5. European Medicines Agency. Chairs of the Scientific Committees. "EMA Regulatory Science to 2025." Published 2020. www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
6. European Medicines Agency. "Quality Innovation Group." September 2023. https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/quality-innovation-group
7. European Medicines Agency. Humans Medicines Division. Quality Innovation Group. "Listen and Learn Focus Group (LLFG) Meeting Quality Innovation Group (QIG)." 13 March 2023. www.ema.europa.eu/en/documents/report/report-listen-learn-focus-group-meeting-quality-innovation-group_en.pdf
8. European Medicines Agency. "International Coalition of Medicines Regulatory Authorities (ICMRA)." September 2023. www.ema.europa.eu/en/partners-networks/international-activities/multilateral-coalitions-initiatives/international-coalition-medicines-regulatory-authorities-icmra
9. "Implementation Plan: ICMRA Pilot Program for Collaborative Hybrid Inspection." September 2023. www.icmra.info/drupal/sites/default/files/2022-06/overall_plan_for_collaborative_hybrid_inspection.pdf
10. American Society of Gene and Cell Therapy. "Read ASGCT's 2023 Q1 Landscape Analysis." 18 April 2023. https://asgct.org/publications/news/april-2023/read-asgct-s-2023-q1-landscape-analysis-field-repo
11. Kingwell, K. "First CRISPR Therapy Seeks Landmark Approval." *Nature* 3 (April 2023). www.nature.com/articles/d41573-023-00050-8
12. Anttonen, E., H. Begi, M. Dubs, I. Helliwell, and J. Selva. "The Development of a Digital Plant Maturity Model to Aid Transformation in Biopharmaceutical Manufacturing," BioPhorum Operations Group. September 2023. www.biophorum.com/wp-content/uploads/bp_downloads/Digtal-Plant-Maturity-Model-White-Paper.pdf
13. "Unified Architecture." OPC Foundation. September 2023. https://opcfoundation.org/about/opc-technologies/opc-ua/
14. National Institutes of Health. "Bespoke Gene Therapy Consortium." 13 June 2023. www.nih.gov/research-training/accelerating-medicines-partnership-amp/bespoke-gene-therapy-consortium

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ISPE thanks the panelists for their presentation. The 2024 ISPE Biotechnology Conference will be 17–18 June in Boston, Massachusetts. For more information or to submit a proposal for the conference, visit ISPE.org/conferences

About the author

Scott Fotheringham, PhD, is a freelance medical and science writer who works with clients in the life sciences. Scott's interests span fields as diverse as pharmaceuticals, biotechnology, molecular genetics, food and beverage manufacturing, and medical cannabis. Scott has been a contributor to *Pharmaceutical Engineering*® since 2015.

Disclaimer: This article contains an abridged, unofficial summary of regulators and industry panelists' responses and discussion during a panel dialogue at an ISPE conference that has not been vetted by any agency or organization. The responses are an informal and brief synopsis of the panel's views, and do not represent official guidance or policy of any agency or organization.

ATMP-Focused Online Seminars Educate and Inspire

By Laura Kuger and Elena Vulpe, PhD

The field of advanced therapeutic medicinal products (ATMPs) has witnessed remarkable advancements in recent years. The Emerging Leaders (EL) community from the Belgium and Germany/Austria/Switzerland (D/A/CH) affiliates collaborated to develop an inclusive series of online seminars on ATMPs. This article gives highlights of the speakers, topics, and knowledge shared in ATMP online seminars over the past year.

Online seminars provide a dynamic, low-barrier tool for education, collaboration, knowledge transfer, and awareness building. These seminars aimed to connect experts from industry, academia, and service providers worldwide, fostering the exchange of ideas, sharing best practices, and discussing the latest advancements, limitations, and potential solutions in the field.

HIGHLIGHTS OF ATMP SEMINARS

ATMP treatments offer promising solutions, including those that are sometimes last resort therapies for previously untreatable and often rare diseases, and help investigate new avenues for personalized treatments. Promoting innovation and ensuring continuity, the dissemination of knowledge regarding these cutting-edge therapies is crucial for researchers, pharmaceutical industry professionals, the general public, and, particularly, future leaders.

Challenges in ATMPs

In the initial seminar, Jasna Curak from F. Hoffmann-La Roche Ltd presented general challenges faced in the field of ATMPs, and Jerome Toussaint and Viridiana Urena from Catalent introduced cell and gene therapy and T cells manufacturing. This seminar effectively highlighted the industry's complexities in manufacturing processes, scalability, regulatory frameworks, compliance, and more, while showcasing practical industry examples of overcoming these challenges.

ATMP Manufacturing Processes

The second online seminar focused on the ATMP manufacturing processes and was delivered by Jørgen B. Magnus, PhD, Tania Pereira Chilima, and Hanna Lesch from Bayer AG, Univercells Technologies, and Exothera, respectively. Each speaker brought a unique perspective, offering alternative solutions to the challenges associated with complex ATMP manufacturing processes. They addressed crucial issues such as scalability, manufacturing infrastructure, and supply chain networks, providing valuable insights and potential solutions.

Tissue Engineering

The third edition of our seminar series shifted focus to tissue engineering. This seminar featured Andreas Eberle, PhD, from CO.DON AG, who discussed the industrial production of cartilage cell therapies. Bert Van den Bogerd, PhD, from the University of Antwerp, provided an overview of the current state of academic research in tissue engineering, bringing a fundamental research and development perspective to the table. This combination of industry and academia leaders addressing applications, manufacturing challenges, and prospects in tissue engineering made the exchange of knowledge extremely fruitful, not only for the participants, but for the speakers as well.

ISPE Guide on ATMPs

ISPE offers numerous advantages to its members, including networking opportunities and the availability of a wide range of educational resources. These resources encompass training, guidelines, and articles that cater to the current trends and needs of the pharmaceutical industry. One such valuable resource is the *ISPE Guide: Advanced Therapy Medicinal Products (ATMPs) – Autologous Cell Therapy*, developed by members of the ISPE ATMP Community of Practice (CoP) and other subject matter experts to assist practitioners in tackling their daily challenges and anticipating future concerns.

During our fourth seminar, Erich H. Bozenhardt from United Therapeutics, Chair of the ATMP CoP, presented the guide and outlined its contents, highlighting use cases, the challenges

addressed in the guide, and the value it brings in supporting the industry. The seminar emphasized the significance and practical support provided by the ISPE Guide in the field of autologous cell therapy manufacturing.

ATMP-Specific Supply Chain Challenges

ATMP-specific supply chain challenges were only briefly touched on in previous seminars, but the fifth one provided a comprehensive exploration of this topic. Alan G. Kelly from Takeda Pharmaceuticals, Inc., the winning company for the 2022 Supply Chain category for the ISPE Facility of the Year Award (FOYA), delivered a remarkable presentation on the Alofisel Global Program. Takeda demonstrated its capability to deliver an autologous cell therapy within an impressive 72 hours, employing a semi-decentralized approach.

Delving further into the future of supply chain operating models, Martin Lippens and Charlotte Meuldermans from Deloitte Belgium shed light on the significance of end-to-end supply chain orchestration and the pivotal role of data- and technology-driven business decision making. This emphasis on efficient supply chain networks will undoubtedly play a crucial role in the industry's growth and development.

Gene Editing

Finally, our most recent online seminar was dedicated to gene editing and its applications. Marc Terrones from the Center for Medical Genetics at the University of Antwerp shared exciting insights into his research in the field of oncology and the development of cancer therapeutics. André Cohnen from Bayer Pharmaceuticals provided an interesting overview of the success stories and collaborations between start-ups and pharmaceutical companies, presented applications beyond oncology, and shared some benefits and ethical considerations for gene editing.

ONGOING LEARNING

These online seminars, organized and hosted by ISPE EL from D/A/CH and Belgium, exemplify the immense value of collaboration across borders and diverse backgrounds. Through our seminars, we successfully transcended barriers and silos—not only geographical ones, but also those stemming from various backgrounds and fields of expertise. This collective effort has fostered a truly inclusive environment, promoting knowledge sharing, innovation, and collaboration in a remarkable manner.

We facilitated low-barrier, direct engagement with leaders and experts through entertaining Q&A sessions and speaker interviews. The seminars therefore also play a crucial role in raising excitement and awareness about certain issues associated with these novel therapies, aiming to inspire and engage young talents to tackle these challenges in their future work.

Laura Kuger is a PhD candidate at Karlsruhe Institute of Technology (KIT), Germany, focusing on continuous, preparative-scale processing for the refinement of ultra-fine particle systems. She holds a master's degree in bioprocess engineering from KIT and has gained industry experience in process development and technology transfer in biopharmaceutical downstream processing. Laura is Chair of the Biotech CoP Process & Data Science subgroup and is a member of the ISPE D/A/CH EL and Women in Pharma. She has been an ISPE member since 2018.

Elena Vulpe, PhD, is a manager at Deloitte focused on IT Quality compliance and regulatory challenges impacting patient safety, product quality and data integrity in the life science industry. She is also an Emerging Leader in the ISPE Belgium Affiliate, where she supports the team with organizing events, disseminating knowledge and connecting students and pharmaceutical industry professionals to foster future leaders' development and promote innovation. She has been an ISPE member since 2020.

New Guidance Document Portal Offers Enhanced Features

In August, ISPE unveiled a new Guidance Documents Portal that provides a significantly improved online user experience for ISPE's full library of Guidance Documents.

Developed in partnership with Wiley, a global leader in scientific publishing, the new portal enables ISPE to improve the effectiveness and impact of ISPE Guidance Documents by leveraging Wiley's global reach, publishing experience, and advanced technologies to help ISPE better achieve our mission. ISPE and Wiley will work together to develop continual advancements.

Benefits of the new portal include:

- Efficiency and ease: Navigate with a fresh, intuitive design for improved user experience.
- Comprehensive search: Access the complete ISPE Guidance Document library effortlessly with enhanced search.
- Adaptable reading: Easily dive into content with an integrated e-reader.
- Seamless mobile access: Experience excellence on any device with responsive design.

To access the Guidance Document Portal, log in to the ISPE.org website and navigate to the Guidance Document Portal. Purchased guides and member benefit guides can be accessed in the My Guides section. Please note that the select ISPE Good Practice Guides included with membership are available for view-only access in the e-reader.

ISPE Unveils First-of-Its-Kind Guidance Document and Launches New Community of Practice on Pharmaceutical Compounding

ISPE is proud to introduce two significant initiatives aimed at benefiting the field of pharmaceutical compounding—the release of the *ISPE Guide: 503B Compounding – Regulatory Basis and Industry Good Practices for Outsourcing Facilities* and the launch of the ISPE Community of Practice (CoP) on Pharmaceutical Compounding.

Regulated by a diverse range of state boards with their own expectations, compounding pharmacies in the United States have historically faced challenges due to the absence of a nationally accepted approach to compliance. The introduction of Sections 503A and 503B to the Food, Drug, and Cosmetic (FD&C) Act in 2013 set regulatory expectations for compounding pharmacies and Current Good Manufacturing Practice (cGMP) outsourcing facilities. In addition, the FDA issued a draft Guidance for Industry in 2020 on the agency's current thinking on regulatory expectations for 503B outsourcing facilities.

ISPE GUIDE: 503B COMPOUNDING – REGULATORY BASIS AND INDUSTRY GOOD PRACTICES FOR OUTSOURCING FACILITIES

In response to industry demands and regulatory complexities, ISPE developed this comprehensive guide to serve as an invaluable resource for 503B outsourcing facilities, aiding them in understanding the regulatory requirements outlined in the FD&C Act Section 503B.

The guide combines FDA regulations and recommendations with pharmaceutical industry standards, providing a go-to document for 503B facilities of all sizes. Various aspects of the compounding process are covered, from the importance of cGMPs to establishing a quality system (including qualifying suppliers and vendors), receipt of raw materials/active ingredients, and shipping of finished drug products.

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

The guide addresses microbiological and analytical testing, including verifying the suitability of compendial methods and validating non-compendial methods. It covers beyond-use dating, offering essential insights into limited stability testing along with stability best practices. A dedicated chapter on preparing for regulatory inspections provides facilities with a valuable resource for this key aspect in ensuring compliance.

We believe these initiatives will play a pivotal role in shaping the future of pharmaceutical compounding, ultimately benefitting patients and communities worldwide.

ISPE COP ON PHARMACEUTICAL COMPOUNDING

The ISPE Pharmaceutical Compounding CoP seeks to foster innovation to improve the practice of pharmaceutical compounding, and to disseminate ideas, knowledge, and best practices through generation of ISPE content, including guidance documents, *Pharmaceutical Engineering®* magazine articles, webinars, blog posts, conference presentations, and training materials.

The new CoP will provide a venue for industry and regulatory informal interactions to drive practical and effective design and operational practices while addressing regulatory expectations and providing solid scientific justification for practices accepted by industry and regulators alike.

Individuals interested in being considered for participation on the newly forming Steering Committee to lead the ISPE Pharmaceutical Compounding CoP are urged to email ISPE at communities@ispe.org

"ISPE is proud to provide critical guidance to the pharmaceutical compounding industry with the release of the *ISPE Guide: 503B Compounding – Regulatory Basis and Industry Good Practices for Outsourcing Facilities* and the launch of the ISPE Pharmaceutical Compounding CoP," said Tom Hartman, President & CEO, ISPE.

"These comprehensive resources signal a transformative step toward fostering collaboration, innovation, and excellence among professionals in this vital sector, and underscore our commitment to advancing knowledge and enhancing compliance within the industry. We believe these initiatives will play a pivotal role in shaping the future of pharmaceutical compounding, ultimately benefitting patients and communities worldwide."

ISPE *Pharmaceutical Engineering*® "Special Report: COVID-19" Honored with 2023 APEX Award

ISPE has been honored with a 2023 APEX Grand Award for Public Health Concerns for the "Special Report: COVID-19."

This award included two articles, "Pandemic Progress: Industry's Journey from 2020 to Today" and "Operation Warp Speed: A View from the Inside." Both articles were published in the May/June 2022 issue of *Pharmaceutical Engineering*®. This marks the fourth consecutive year that *Pharmaceutical Engineering*® has received an APEX Award.

The APEX Awards commend excellence in writing, editing, and graphics across a wide range of communications in nonprofit and for-profit publishing and communications organizations. Awards of Excellence recognize exceptional entries in 100 subcategories, and Grand Awards honor outstanding work in 14 major categories.

"Pandemic Progress: Industry's Journey from 2020 to Today" explores the remarkable evolution of the healthcare and pharmaceutical industry's response to the COVID-19 pandemic, highlighting the rapid development of vaccines, collaborative efforts among competitors, and advancements in understanding the virus. The article was authored by ISPE member, Wendy Haines, PhD, DABT, CQA, Director of Toxicology & Technical Services, PharmEng Technology.

"Operation Warp Speed: A View from the Inside" provides an inside look at the work done by Operation Warp Speed, a US government initiative supporting the accelerated development and supply of vaccines and therapeutics across the United States to address the threat posed by COVID-19. The article was written by Carlo de Notaristefani, PhD, Consultant, who assumed the role of lead advisor for Manufacturing and Supply Chain at Operation Warp Speed/Federal COVID Response in May 2020.

Facility of the Year Awards Honor Groundbreaking Facilities

Since 2005, ISPE's Facility of the Year Awards (FOYA) have recognized state-of-the-art projects utilizing new, innovative technologies to improve the quality of products, reduce the cost of producing high-quality medicines, and demonstrate advances in project delivery.

Each year, submissions are accepted from projects worldwide, representing breakthroughs in various disciplines, from automation and integration to the development of medicines for underserved populations. Ultimately, a panel of industry leaders chooses the projects that set the standard to receive FOYA in the categories of Innovation, Operations, Supply Chain, Pharma 4.0™, and Social Impact.

MEET THE 2023 FOYA CATEGORY WINNERS

From a facility making groundbreaking advancements in sustainability practices, including a goal to be carbon net zero by 2030, to a vaccine manufacturing facility that produced hundreds of millions of doses of COVID-19 vaccines, 2023's FOYA Category Winners represent leadership and innovation that span the globe.

Innovation: FJ2 Project, Chugai Pharma Manufacturing Co., Ltd.

Winners of the Innovation FOYA category exemplify the novel application of process manufacturing techniques, innovative design concepts, new technologies, and unique solutions, demonstrating the next generation of pharmaceutical and biotechnology facilities. Chugai Pharma Manufacturing Co., Ltd.'s FJ2 is an API facility built for the manufacture of small and mid-size molecule drugs to be used for clinical development purposes. Located in the heart of Japan at a key transportation point, the construction and commissioning of the manufacturing center were completed in August 2022.

Chugai is notable for its focus on safety throughout the entire project design. The FJ2 facility has several innovative building design and equipment concepts implemented to protect both the product and the worker. This includes isolators applying smart containment technology developed by JGC, world-class high potency containment technology, and design considerations for even the worst-case scenarios such as destructive earthquakes.

Operations: WuXi Biologics CRDMO Ireland, WuXi Biologics Ireland Limited

The WuXi Biologics facility in Dundalk, Ireland, is a contract research development and manufacturing (CRDMO) facility. This project exemplified the category's focus on the application of novel tools and approaches to deliver projects that improve efficiencies, overcome unusual challenges, promote effectiveness, and organize stakeholders and project team participants with successful outcomes.

The facility deploys hybrid, single-use, scale-out production technology for multiproduct mAb and recombinant protein drug substances and houses innovative manufacturing science and technology labs to support customers with manufacturing capacity and product research and optimization.

Not only is the 467,000-square-foot greenfield facility one of the largest facilities of its kind in Europe, with two manufacturing areas utilizing 6 x 1KL single-use (SU) bioreactors for perfusion and 12 x 4KL SU fed-batch bioreactors, the facility was brought to fruition in record time while overcoming a series of challenging circumstances. These included ensuring the safety of the project team during the height of the COVID-19 pandemic, the discovery of archaeological remains on the project's site dating to the Neolithic period, and undertaking significant efforts to reduce construction and traffic impacts on neighbors.

Supply Chain and Social Impact: NISHWAS "The Breath of Relief," Serum Institute of India Pvt. Ltd.

The Serum Institute of India Pvt. Ltd's NISHWAS project was awarded two 2023 FOYA Category wins—Supply Chain and Social Impact. Not only did the NISHWAS project exemplify the application of principles, systems, and management tools aimed at improving operational speed, robustness, and response under time constraints, but the project also had an extensive impact on the well-being of millions of people.

Serum made the exceptional accomplishment of producing COVID-19 vaccines at a commercial scale in six months, beginning design modification on 1 October 2020, and rolling out the first batch of vaccines on 31 March 2021. This was made possible despite the challenging work environment created by the ongoing COVID-19 pandemic through real-time project risk management and close multi-disciplinary coordination.

Ultimately, Serum supplied over 1.47 billion doses of Oxford–AstraZeneca's Covishield vaccine in 2021 and 276 million doses in 2022. During the same period, Serum manufactured and supplied more than 9 million doses of Novavax's Covovax/Nuvaxovid COVID-19 vaccine in 2021 and 129 million doses in 2022. By the end of 2022, Serum had supplied COVID-19 vaccines to over 90 countries.

Pharma 4.0™: South San Francisco Clinical Supply Center, Genentech

Winners in the Pharma 4.0™ category embody the Pharma 4.0™ concept, often referred to as continued innovation and integration of digitalization and automation. However, Pharma 4.0™ is more than an automation system or interconnective facility; it is the end-to-end integration and optimization of systems and processes throughout the facility.

Genentech's South San Francisco Clinical Supply Center is a 78,000-square-foot/2,000-L-scale, small-volume clinical biologics facility that was completed in 19 months. The facility is recognized as a role model in applying bold objectives, deep alignment, end-to-end planning, and innovation in using digital technologies. The resulting facility delivers improved outcomes in construction, safety, productivity, and patient access to innovative medicines.

Notable facility highlights include fully integrated automation, robotics, and operations management systems; rapid response and agility goals that are aligned with clinical supply chain optimization; the ability to easily scale from a single batch to campaigns in the same facility; and full digital validation and a paperless manufacturing operation.

Social Impact—Sustainability: Glassia Manufacturing Building, Takeda SA

Takeda's Glassia Manufacturing Building in Lessines, Belgium, won for its application of innovative sustainability technologies and focus on the effective use of resources to reduce environmental impact, including a goal to be carbon net zero by 2030. The Glassia Manufacturing Building approaches sustainability at every level, from the supply of raw materials to the production of its therapies, to the shipment of its vials of finished products to over 80 countries. The entire value chain is continually analyzed to reduce its footprint wherever possible.

Takeda's Lessines site is the first pharmaceutical manufacturing site in the world to recycle its wastewater to drinking water standards and reuse it in the production process. The site is also entirely paperless, engages extensive waste management procedures, has over 8,000 solar panels installed (with plans to install more in coming years), and plans to employ geothermal wells and two wind turbines to help it meet its carbon net zero goals.

In addition to sustainability efforts, social initiatives have been undertaken at the facility, including collecting and delivering medical devices to Ukraine, road clean-up activities around the site to safeguard the environment, and volunteering days organized to help local associations.

> From a facility making groundbreaking advancements in sustainability practices, to a vaccine manufacturing facility that produced hundreds of millions of doses of COVID-19 vaccines, 2023's FOYA Category Winners represent leadership and innovation that span the globe.

Honorable Mention: Project Tomorrow, Nexus Pharmaceuticals, Inc.

The Honorable Mention category recognizes projects that did not win a specific category but were successful while overcoming significant challenges in planning, execution, and delivery. Nexus Pharmaceuticals is a uniquely American family company, built on the dreams of its founder, Mariam S. Darsot, to fill a gap in the market to develop better products at lower costs for consumers. Nexus specializes in developing priority generics, such as hard-to-formulate, critical-need molecules that are routinely in short supply. Project Tomorrow showcases Nexus Pharmaceuticals' consistent focus on meeting patient needs for the long term.

The facility currently employs state-of-the-art isolator technology, two vial-filling suites, and the capability to produce aseptic, terminally sterilized, and lyophilized products. While establishing an impressive design and technology aligned with current industry standards, Project Tomorrow also includes thoughtful plans for maintaining quality standards as facility capacity and capability expand to support up to six fill lines. Delivering these capabilities as a small, family-owned generic company showcases their commitment to patients and their company mission.

SUBMIT YOUR MATERIALS FOR THE 2024 FOYA

Has your company recently designed, built, or renovated a best-in-its-class, state-of-the-art pharmaceutical or biotechnology facility? Submitting your facility for a FOYA is an opportunity to showcase your team's hard work and innovation within the pharmaceutical and biotechnology manufacturing industries. Final project submissions are due 4 December 2023. Submit at ispe.org/facility-year-awards/submit

Meet the ISPE STAFF

VICTORIA BUCCI

In each issue of *Pharmaceutical Engineering*®, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Victoria Bucci, Digital Marketing Manager on the Marketing team.

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

Day-to-day I manage paid advertising efforts, social media accounts, and curate ISPE content for the SmartBrief newsletters.

What do you love about your job?

I love the wide variety of content available to pull from. Not only do we have regular blog articles and PE magazine editions, but each team also has something for me to help promote. This gives me a chance to test new paid advertising strategies, keep our social media channels active, and share valuable updates and information with our SmartBrief subscribers.

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

Outside of work, I spend a lot of time camping with my husband and our friends. We enjoy getting away for a short weekend of hiking, kayaking, and sitting by a fire. We also love going to comedy shows. We have five planned so far for the rest of the year.

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BENEFITS AND CHALLENGES of Process Capability Metrics

By Tara Scherder, James Crichton, Andreas Dander, PhD, and Mahesh Shivhare, PhD

Process capability is a fundamental concept for manufacturers. Pharmaceutical, biopharmaceutical, and medical device manufacturers leverage capability analysis along with other statistical quality control (SQC) techniques to enable timely supply of quality medicine to patients.

Process capability is defined in ASTM E2281 as "the natural or inherent behavior of a stable process that is in a state of statistical control" [1]. Process capability analyses typically compare process behavior to customer needs. Metrics such as capability and performance indices reflect the ability of a manufacturing process to deliver a product meeting the required specifications.

CAPABILITY ANALYSIS IN PRACTICE

Although the formulas for capability indices are relatively simple, real-life application can be challenging due to complexities that are not included in simple textbook examples. For instance, statistical control is not necessarily expected when data fail the underlying assumption of a random homogenous distribution, which commonly occurs in pharmaceutical manufacture because of autocorrelation or subpopulations. Approaches for limited data and non-normality must also be considered, as well as the derivation of specifications.

Ultimately, pharmaceutical, biopharmaceutical, and medical device manufacturers use capability analysis along with SQC techniques to supply patients with the right medicine, at the right time, and at the right cost. In addition to the obvious requirement of ongoing product quality, achieving this comprehensive patient goal depends on efficient use of organizational resources. The use of process capability (as one tool among others) to manage product quality risk and prioritize resources has been discussed in previous ISPE publications.

Allison et al. proposed a process capability maturity model that includes a risk-based approach to process capability which "prioritizes and applies resources where they are needed most to enhance patient safety, guarantee compliance, ensure efficient use of resources, and drive business value" [2]. The ISPE Process Capability Team describe the role of process capability metrics in process monitoring and product robustness efforts as "most meaningful as a tool to proactively identify risk of out-of-specification results" [3]. In this article, we focus on the practical details of this utilization.

We begin with a foundational section including discussion of relevant nuances for the mentioned industries, followed by a practical implementation of process capability metrics for risk assessment enabling appropriate prioritization and control, and end with case studies of real-world utilization of process capability.

CONCEPTS AND DEFINITIONS

Process Capability Indices

Process capability is commonly described as the ability of a process to deliver a product that meets customer needs. More specifically, it is the comparison of a fixed quality range (specification range) with the manufacturing range (spread of process data). Process capability indices condense this comparison into a single, dimensionless metric generally defined as:

$$Process\ capability\ index = \frac{specification\ range}{spread\ of\ process\ data} \qquad \text{Eq. (1)}$$

These indices can be translated to a quantifiable risk (e.g., percent defective) when underlying statistical assumptions are met. It is easily seen that risk decreases as the index increases. That is, as the relative width of the process variability decreases compared to the specification range, there is less risk of producing a product out-of-specification (OOS) limits.

The exact computation of process capability indices depends on the method used to estimate variability (standard deviation) and whether data centrality with respect to specification limits is incorporated. The following section describes commonly used process capability indices in the pharmaceutical, biopharmaceutical, and medical devices industries.

Process Capability Indices P_p, P_{pk}, C_p, and C_{pk}

Process capability can reflect short-term or long-term expectations. The computation of process variability distinguishes the two, not the sample size or referenced time. Long-term estimates of process capability use the sample standard deviation to estimate process variability, symbolized by $\hat{\sigma}_{LT}$. The long-term index, P_p, is the ratio of the specified fixed quality range—difference between the upper specification limit (USL)

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and lower specification limit (LSL)—and the spread of the process data ($6\hat{\sigma}_{LT}$). It quantifies the potential of process output to fall within a specified range.

$$P_p = \frac{USL-LSL}{6\,\hat{\sigma}_{LT}} \qquad \text{Eq. (2)}$$

where $\hat{\sigma}_{LT} = \sqrt{\sum_{i=1}^{n} \frac{(x_i-\bar{x})^2}{n-1}}$

The long-term index P_{pk} takes into account the location of the data and quantifies process performance with respect to the nearest specification.

$$P_{pk} = minimum\left\{\frac{USL-\bar{x}}{3\,\hat{\sigma}_{LT}}, \frac{\bar{x}-LSL}{3\hat{\sigma}_{LT}}\right\} \qquad \text{Eq. (3)}$$

Short-term process capability is estimated by replacing $\hat{\sigma}_{LT}$ in equations (2) and (3) with a short-term estimate of variability, derived from the moving range between consecutive results when individual results are trended. The short-term indices, C_p and C_{pk}, are thus computed as:

$$C_p = \frac{USL-LSL}{6\,\hat{\sigma}_{ST}} \qquad \text{Eq. (4)}$$

$$C_{pk} = minimum\left\{\frac{USL-\bar{x}}{3\,\hat{\sigma}_{ST}}, \frac{\bar{x}-LSL}{3\hat{\sigma}_{ST}}\right\} \qquad \text{Eq. (5)}$$

C_{pk} represents the capability if the long-term shifts in the process were removed. More detail on the concepts and computation of capability indices can be found in Montgomery [4] and Wheeler [5].

Difference Between Long-Term and Short-Term Sigma

If a process is stable and homogenous (data can be described by single distribution) then long-term ($\hat{\sigma}_{LT}$) and short-term ($\hat{\sigma}_{ST}$) sigma/standard deviation will be equivalent. However, if data are not homogenous, these two estimates can be quite different. Non-homogeneity could result from mean shifts with known cause (e.g., production campaign influences, bulk quality control [QC] analysis, or different raw material suppliers) or autoregressive effects (e.g., equipment wear and seasonal drifts). If these issues are cause for concern during manufacturing, and identification of small shifts or drifts is sought, then use of short-term deviation ($\hat{\sigma}_{ST}$) is appropriate for both control charting and process capability estimation, and C_p and C_{pk} should be applied.

On the other hand, if the non-homogeneity or detectable patterns or trends are expected as an intrinsic part of the process, use of long-term standard deviation ($\hat{\sigma}_{LT}$) estimate is likely more appropriate. Not only will P_p and P_{pk} represent the actual performance given all the observed variation in the process, but this choice will also result in more suitable long-term control limits. Non-homogeneity is quite common in pharmaceutical and device manufacturing due to multiple restrictions within process improvement, including, but not limited to, limitations to control raw material quality, complicated supply chains, complex manufacturing and analytical processes, batch campaigns, and regulatory constraints and efforts. Thus, performance indicator P_p or P_{pk} is generally appropriate.

Knowledge of actual performance is of primary importance when using process capability metrics to assess risk and prioritize resources, compared to the potential process capability that could be possible if shifts and trends that occur over the longer term were removed. Consider an analogy in the sports world. A team may have the greatest potential on paper based on individual player statistics but it's their overall performance that really matters. And if this performance is inadequate, then further study to understand the gap between potential and actual performance is warranted.

Table 1: Predictive OOS risk for estimated P_{pk}.

C_{pk} or P_{pk}	OOS Risk (One-Sided)*, %
0	50.00
0.5	6.68
0.6	3.59
0.7	1.79
0.8	0.82
0.9	0.347
1	0.135
1.1	0.0483
1.2	0.0159
1.33	0.0032
1.5	0.00034
2	0.0000001

*Note this risk is one-sided. For a rough estimation of two-sided risk, multiply the OOS risk by a factor of 2.

Failure Rate Prediction

Capability indices can be directly translated to the OOS risk listed in Table 1 *if* certain statistical assumptions are met, specifically normality and independent and identically distributed (IID) data.

If these assumptions are not met, the estimated OOS risk/defective rates in Table 1 will not be accurate. However, if indices are primarily leveraged to assess risk with commensurate action, this inaccuracy may be tolerable. If the reason for failure to meet assumptions cannot be identified or is due to the intrinsic nature of the parameter (e.g., campaign effect, autocorrelation due to bulk testing or raw material usage, bounded data, etc.), subject matter experts (SMEs) must determine the risk prediction qualitatively, which is further discussed next.

Influence of Derivation of Specification Limits

In typical industrial applications, specification limits are directly based on customer needs. Because the in vivo mode of action cannot always be translated to simple numerical ranges, this is often not possible, particularly for biopharmaceutical products. Also, it is not

Table 2: A proposal for a risk classification system using P_{pk}.

Risk Evaluation Capability Criterion Threshold	Risk Category (Risk of OOS)	Additional Risk Evaluation	Management Response
$P_{pk} \geq 1.33$	Low	None; decrease in monitoring intensity level may be appropriate	Low risk to product, hence no response
$1.33 > P_{pk} \geq 1.0$	Medium	Further statistical analysis and/or judgment by SMEs may be required to verify or adjust risk category	Medium to low risk to product, hence no response
$P_{pk} < 1.0$	High	Thorough statistical analysis by SME to verify or adjust risk category; detailed investigation may be warranted to determine appropriate risk control	Aware of the associated risk to product and supply chain; support and provide resources for any investigational and/or remediation activity

common practice, nor is it necessarily feasible or desirable, to design clinical trials to have a range of quality attribute results reflecting expected manufacturing process capability.

This lack of patient-centric specifications and guidance in ICH Q6B [6] leads to the common practice of using the actual process performance from the limited process development and clinical batches to compute acceptance criteria for the product specifications. These acceptance criteria (commonly termed specification limits and used as such in process capability computations and software) are often derived using either a tolerance interval or simple mean +/- 3*standard deviation approach. These approaches can lead to conservative (narrow) limits and limit the P_{pk} to a value of 1 (a 3-sigma process).

Additionally, this approach can have serious consequences, as natural deviations in manufacturing and analytical measurement that occur in the commercial supply stage are not considered in the initial specification limit estimation process. Additionally, internal release limits (IRL) designed to account for potential change during shelf life of the product will often further reduce the acceptance range. It is critical to understand the effect these two practices have on process performance metrics, and seemingly poor performance of the pharmaceutical industry compared to other industries where specification limits are independent of process performance.

PRACTICAL IMPLEMENTATION OF PROCESS CAPABILITY

Ultimately, the primary purpose for capability and performance analysis is ongoing risk assessment and commensurate control aligned with the quality risk management process described in ICH Q9 [7]. More specifically, process capability metrics are used to analyze the risk to product quality by estimating the likelihood of OOS results. The understanding that the relationship between and likelihood of OOS results is nonlinear is crucial to evaluation of that risk. Table 1 highlights that small changes in for values < 1.0 have a marked effect on the likelihood of OOS results, whereas a negligible increase in expected OOS results occurs for changes when P_{pk} is greater than 1.33. With this understanding, risk evaluation such as the grid of Table 2 can be properly designed.

It is often reasonable to assign low risk to processes with P_{pk} values > 1.33, given the expected number of results exceeding specification limits is small (< 0.006%) for values above this threshold. The criteria identifying medium risk and high risk are key, given critical decisions might be made for these levels. These thresholds and related actions are approved by management.

Criteria in addition to the OOS risk could be included to determine the details of each risk category, such as product volume, medical need, supply chain risk, and product cost. For instance, adjustment of the capability criteria in Table 2 to trigger earlier action may be warranted for a high-volume product, or one having critical patient need. Further details of this table are provided in following discussions.

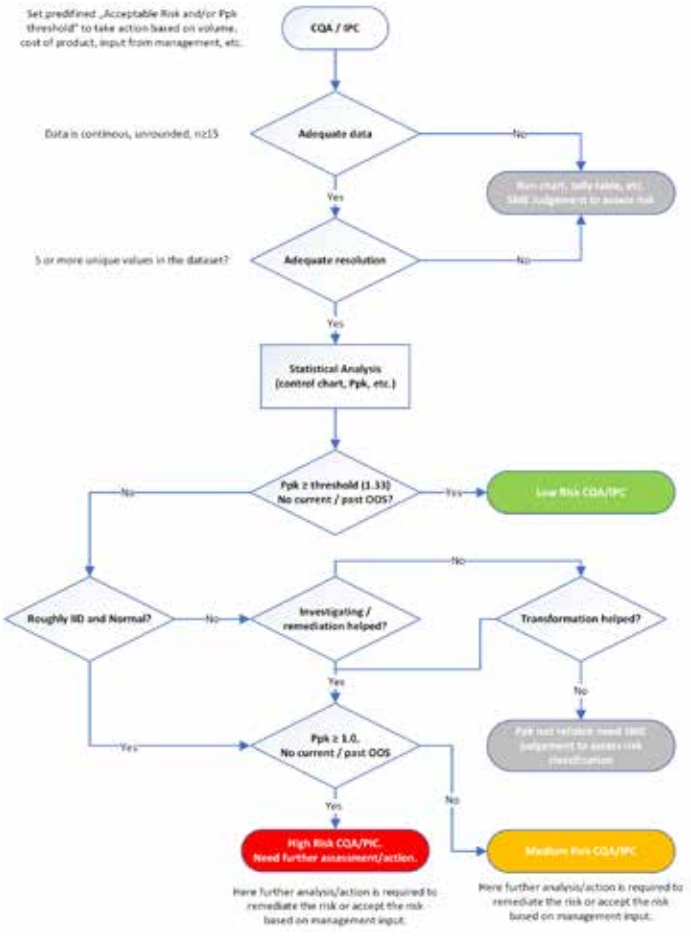
Typical Process Capability Application Process in Pharmaceutical Industry

Once the variables to be monitored have been identified (relevant critical quality attributes [CQAs], in-process checks, critical process parameters, and critical material attributes), and management has defined thresholds and actions for each risk category, process capability can be leveraged in a risk assessment of process performance. Before process capability is computed, potential influences of the data must be accounted for, such as:

- What is the scope of the data or the data window? Does it use specific dates, such as last quarter or last year, or is it based on a specific count, such as the last 15 batches?
- Has the data been modified, for instance to remove outliers? Is this elimination justified?
- Is the data in meaningful time order, such as manufacturing run order or testing date?
- What is the influence of the measurement system?
- What is the unit level? For instance, is the measurement an individual or average result?
- What data characteristics could influence process capability interpretation?

Once data influences are understood, process capability metrics can be used as a tool for risk assessment of ongoing product quality

Figure 1: Example flow chart to aid the practical use of process capability for risk management and prioritization.



and hence prioritization of resources. Figure 1 displays this risk assessment and associated actions. This sample flow chart includes statistical decisions related to several common nuances of pharmaceutical manufacturing data.

To properly analyze performance risk using process capability metrics, data must meet the following requirements of both sample size and data resolution.

Sample size

There is no magical sample size that is appropriate for every application. It is recognized that P_{pk} can be unstable until 60 to 90 results have been incorporated. However, this amount of data could take years of production or be completely unfeasible for low-volume products. Thus, to enable a risk-based approach as described in Table 2, P_{pk} can be computed for data sets as small as 15 data points. However, in such instances, the P_{pk} values should be considered tentative and the influence of the small sample size on prediction accuracy should be recognized in risk evaluation. If possible, sample size can be increased by extending the historical data window. If this is not plausible, or is unreasonable due to process changes, the performance of a process with limited data can be practically interpreted by an SME with run charts annotated with specifications.

Data resolution

Inadequate data resolution results in increased uncertainty in the estimate of standard deviation [3]. A general rule of thumb is that a data set must include at least five unique values, quickly confirmed with a simple dot plot. Whenever possible, it is best practice to evaluate data in raw, unrounded form because rounding can cause low resolution. Like inadequate sample size, run charts annotated with specification limits for practical interpretation by SMEs are recommended for cases of inadequate resolution.

Once adequate data with adequate resolution is available, P_{pk} can be computed and used in an evaluation of risk using categories such as those in Table 2. More detail for the risk categories and the influence of data assumptions follows.

Low-Risk Attributes

Low-risk attributes with P_{pk} of 1.33 or higher need no further statistical analysis or action. Resources are better spent on parameters

categorized as higher risk, or other more value-added activities. Depending on site governance and the current monitoring practice, reduction in the monitoring level of such low-risk attributes may be warranted.

Medium-Risk and High-Risk Attributes

For medium-risk or high-risk attributes, further analysis (e.g., a control chart, histogram with specifications, and a normal probability plot) should be performed to obtain a more precise understanding of the risk. For attributes in these categories, understanding the influence of the two underlying assumptions of IID data and normality are essential to proper risk evaluation.

IID Data

The control chart can be used to practically evaluate the IID assumption that underlies the translation of P_{pk} into a risk of OOS. It is not uncommon to observe multiple clusters of data because major sources of variability, such as raw materials, are not experienced randomly. In these cases, the assumption of a single population of independent results is not met, and estimation of a single P_{pk} value may be unreliable. Automated processes also often exhibit non-independence, evidenced by autocorrelation in control charts. Separating a control chart by stages (a potential factor responsible for a lack of IID, such as campaign, laboratory, raw material, etc.; example is shown in case study 3) may identify the cause for failure of the IID assumption.

Non-Normality

Non-normality also impacts the accuracy of the estimated risk from P_{pk} values. Visual probability plots are recommended to assess normality instead of reliance on a p value from formal statistical tests such as the Anderson–Darling or Kolmogorov–Smirnov tests. If the assumption of IID is not met, then a normality test is irrelevant. If the data are not normal, several alternatives are possible for estimating risk, including data transformation, fitting an alternative distribution, or using a nonparametric approach.

However, data transformation should be applied only when the reason for non-normality is understood (inherent to the nature of the measurement) and behavior is predictable. Complex transformation procedures, such as the Johnson transformation, are difficult to explain and justify and should be avoided. Non-parametric approaches require large sample sizes to obtain reasonable confidence. When the underlying distribution is not known to be inherently non-normal, often the most reasonable approach is to assess the practical significance of the non-normality. For instance, the P_{pk} may be so high that the inaccuracy caused by non-normality is inconsequential. Or the skewness that influences the P_{pk} may be in the opposite direction of the closest specification.

Potential Treatment of Violation of Statistical Assumptions

If potential reasons for the violation of IID data and normality assumptions are identified (e.g., campaign effect), then control charts and process capability should be plotted and estimated appropriately (e.g., plot and estimate control chart and process capability respectively by campaign and scrutinize performance of latest campaigns). However, if potential reasons cannot be identified or failure of IID or normality assumptions is due to the basic nature of the variable (e.g., lower bound in case of impurity), the level of risk is left to the judgment of SMEs. There are several options to evaluate performance in these situations, including:

- Assess the distance of results to specification limits (e.g., actual results more than one standard deviation from the closest specification limit combined with no OOS results in the last three campaigns could reduce the risk category).
- Evaluate recent performance or trend in context of historical performance (e.g., recent campaigns operating closer to specification limits compared to past campaigns could translate to high risk).
- Compare performance after process change to historical performance (e.g., after recent corrective and preventive action [CAPA] implementation, a process that has moved farther from specification could reduce risk category).
- Compare actual performance to that predicted by the normal distribution using the mean and standard deviation of the data (e.g., skewness that results in actual performance better than predicted by the computed normal distribution could reduce the risk category, whereas results closer to the nearest specification than a normal distribution would predict could translate to high risk).

In addition to more rigorous statistical analyses, additional cross-functional investigation is often warranted for high-risk attributes to avoid OOS results. Risk control ranges from increased monitoring frequency to remedial actions to reduce risk.

It is quite common that the underlying assumptions are not met. It is critical to understand that textbook application is not to be expected, requiring interpretation that combines both statistical and process knowledge, along with relevant business and patient influences. To demonstrate real-life application of the flow chart in Figure 1, the next section provides case studies of the practical use of to analyze product quality risk and prioritize resources for common situations of complex, non-textbook-type data.

CASE STUDIES

Case Study 1: Stable, Normal Process

A process capability analysis [8] of assay results from 30 batches with LSL = 90 and USL = 110 is shown in Figure 2. There is adequate data with acceptable resolution and no notable trend or distribution features. The estimated P_{pk} of 1.97 is greater than the predetermined threshold of 1.33. According to the flow chart, this attribute can be classified as high performing, representing a low risk of OOS results, and no further analysis is needed.

If specifications of 95%–105% were applied to the same data, the P_{pk} would decrease to 0.88, and the reliability of the P_{pk} needs to be considered. Based on the control chart (stable and random), the histogram and normal probability plot, the data adequately meet

Figure 2: Sixpack capability analysis to evaluate assumptions and assign risk category.

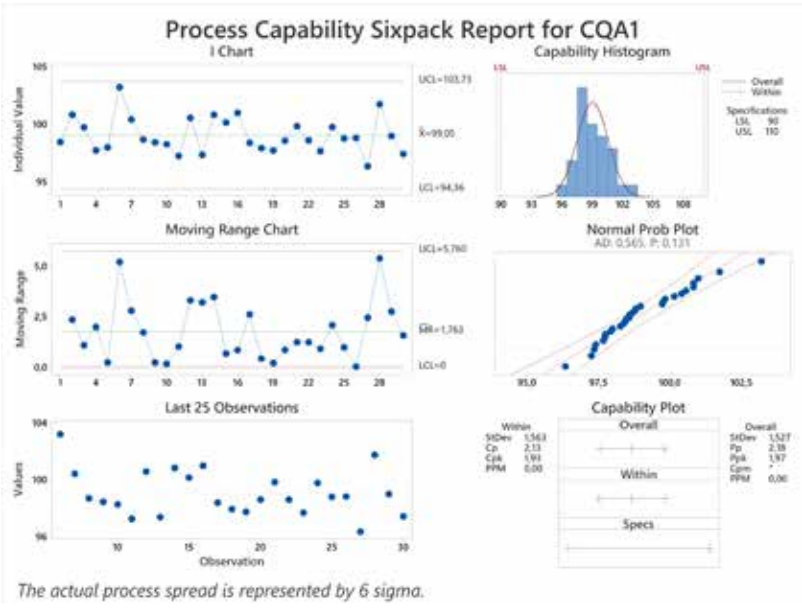
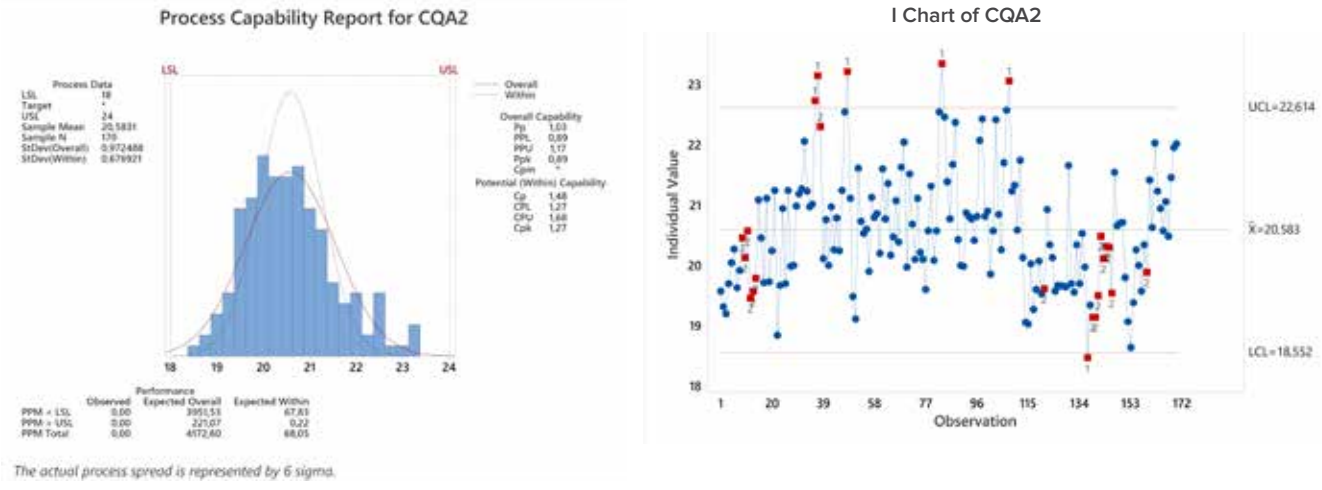


Figure 3: Capability analysis indicating violation of the IID assumption; hence, the risk prediction is unreliable.



assumptions of IID and normality. Hence, the estimate of P_{pk} is reliable and the high-risk category would be assigned.

Case Study 2: Autocorrelated Process

Process capability analysis revealed a P_{pk} of 0.89 (see Figure 3). However, there is evidence of autocorrelation in I-chart (process drifting and/or shifting) that invalidates the IID assumption. The multiple subpopulations inflate the long-term standard deviation, resulting in a deflated P_{pk}, whereas the short-term estimate derived from the moving range and used to estimate C_{pk} underestimates the overall variability. Thus, the true capability of the process is somewhere between the P_{pk} and C_{pk} values; see the discussion of equations (2)–(5). Note that the overlaid normal distribution using the long-term (overall) standard deviation overestimates the amount of results in the left tail of the distribution.

Although addressing the cause of the subpopulations could lead to increased process capability, this parameter could be classified as medium risk given the distance of the majority of the data to specification, there are no results within 0.5 units of specification (equal to about 0.5 standard deviation), and there were no OOS

Figure 4: Control charts of the CQA with distinctive subpopulations.

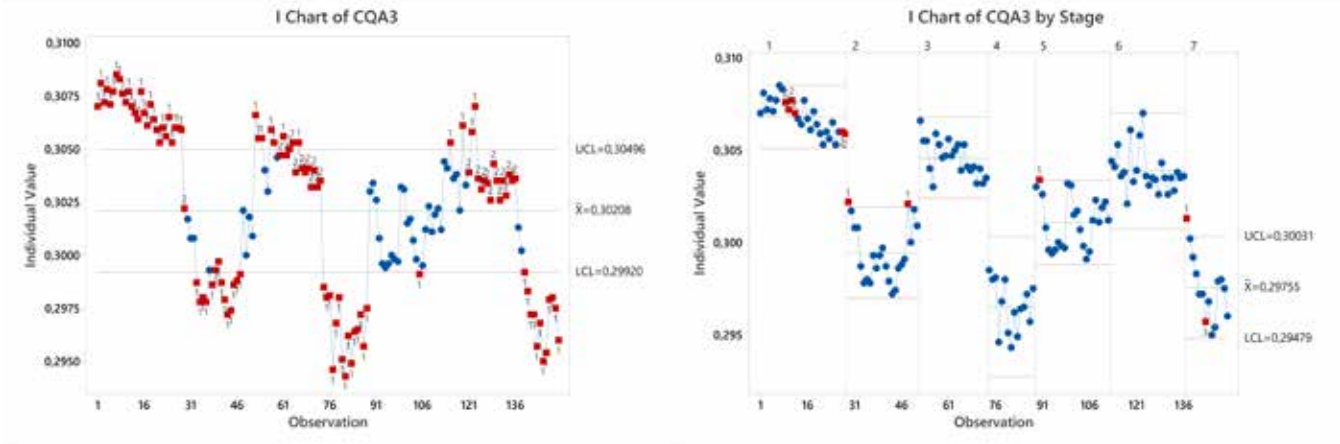
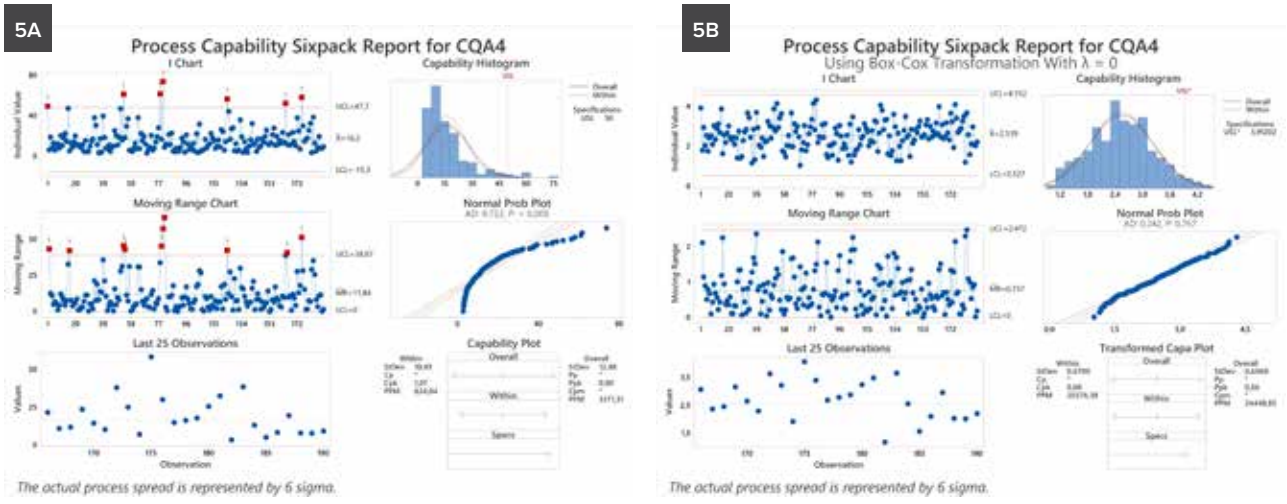


Figure 5: Sixpack capability analysis (A) suggesting that IID and normality assumptions are violated and the risk prediction is unreliable, and (B) after log transformation showing that IID and normality assumptions are valid, the process is stable and predictable, and the risk prediction from 0.66 is reliable.



results in the 170 batches. A detailed investigation is not warranted; risk control actions would be limited to (possibly) increasing the frequency of monitoring.

Case Study 3: Process with Shifts

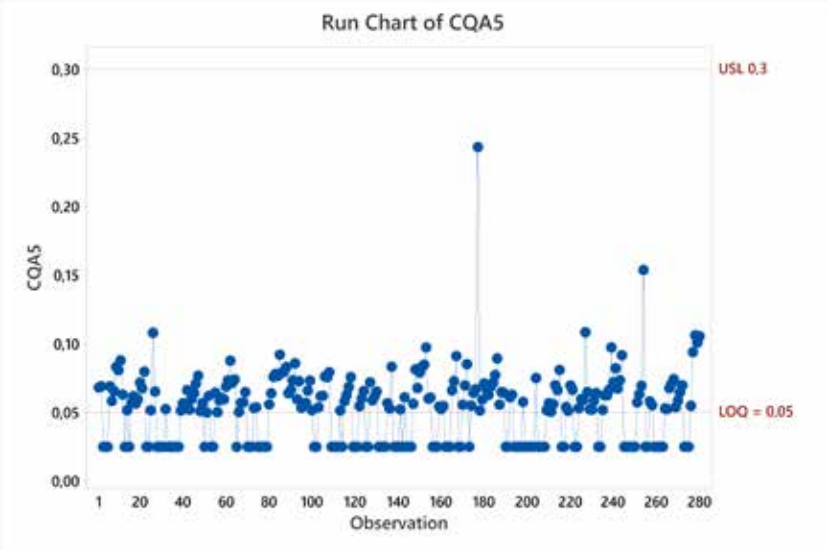
Unlike the previous example, the pattern in the control chart in Figure 4 has distinct, nonrandom clusters of data, possibly due to campaign-to-campaign variation, raw material changes, QC testing series, etc.

Hence, these data violate the IID assumption, and control limits and the P_{pk} of 0.72 computed using the entire dataset are unreliable (capability analysis not shown). The likelihood of failure is much lower than associated with this P_{pk} value. In this case, the C_{pk} value of 2.75 considering the process capability by subpopulation more accurately reflects the overall likelihood of failure. The high capability by subpopulation is obvious in the control chart split by campaign, where control limits are well within the USL of 0.31. Although there is opportunity to improve the consistency of this parameter by identifying the cause of the shifts, the motivation should not come from a need to improve overall P_{pk}, as the true capability risk is medium to low.

Case Study 4: Non-Normal Data

The evaluation of 183 batches of a parameter with an upper specification of 50 units led to a P_{pk} of 0.90. The sixpack analysis (see Figure 5A) showed that both IID and normality assumptions were violated, leading to an unreliable P_{pk}. The data have a lower bound of 0 units and are skewed to the right. The underlying distribution is truly non-normal; hence, a transformation is appropriate. A log transformation resolved IID and normality issues

Figure 6: Run chart with censored data of LOQ = 0.05.



When the influence of process nuances and data characteristics is understood, an effective risk-based approach to quantify risk and prioritize resources using process capability metrics is possible.

(see Figure 5B). The transformed specification limit of 3.912 units results in a reliable of 0.66. This low value in addition to seven OOS events translate to high risk, and this parameter is identified for process improvement.

Case Study 5: Censored Data

Censored data are a common issue with measurements of byproducts and biological impurities, due to many results being less than the limit of quantification or detection (< LOQ or < LOD). A summary article written by Haas and Scheff [9] compares different methodologies for the estimation of the true mean and standard deviation for data sets containing results below a known detection limit. Such methods can be useful to derive P_{pk}, but should be applied only in cases where less than 50% of the data are censored. In many cases of censored data, as in this case study, computation of P_{pk} is not necessary to assess risk. In Figure 6, it is clear that the risk of exceeding the specification limit is low based on the annotated run chart. In such cases, the metric % < LOQ across a fixed number of batches could be useful to evaluate ongoing performance.

CONCLUSION

The assessment of process capability is critical to assure ongoing product quality and assign resources to products with higher risk of supply and regulatory risk. It can easily be incorporated into a risk-based approach to evaluate process performance and plan commensurate actions.

Although the formulas for common process capability metrics such as C_{pk} and P_{pk} are simple and intuitive, the accuracy of these estimates relies on underlying assumptions for the data and associated process. Because these assumptions are often not met in pharmaceutical manufacturing, assessing process capability in this environment can be more complex than a simple metric. These cases require a deeper understanding of the data, including the influence of the data structure on the estimate of the process capability index. Additional evaluation may also be required. In many cases, the risk assessment is limited to a practical evaluation of process capability by the SME.

When the influence of process nuances and data characteristics is understood, an effective risk-based approach to quantify risk and prioritize resources using process capability metrics is possible. This approach ensures product quality and limits wasteful activities, thus aligning with the patient needs of the "right medicine, at the right time, at the right cost."

References

1. ASTM International. *ASTM E2281 - 15(2020): Standard Practice for Process Capability and Performance Measurement.* West Conshohocken, PA: ASTM International, 2020. doi:10.1520/E2281-15R20
2. Allison, G. A., P. Cini, G. Leister, E. R. Montgomery, J. O'Neill, P. Stojanovski, and A. Zilian. "How Robust Is Your Process Capability Program?" *Pharmaceutical Engineering* 38, no. 1 (January/February 2018).
3. ISPE Process Capability Team. "Role of Process Capability in Monitoring Product Quality: Monitoring Requirements and Self-Audit Continuous Improvement Opportunities." ISPE Concept Paper, 12 May 2017.
4. Montgomery, D. C. *Introduction to Statistical Quality Control,* 8th ed. New York: John Wiley and Sons, 2019.
5. Wheeler, D. J. *The Six Sigma Practitioner's Guide to Data Analysis*, 2nd ed. Knoxville, TN: SPC Press, 2010.
6. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline. Q6B: Specifications: Test Procedures and Acceptance Criteria for New Biotechnological/Biological Products." Published March 1999. https://database.ich.org/sites/default/files/Q6B_Guideline.pdf
7. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q9: Quality Risk Management." Published November 2005. https://database.ich.org/sites/default/files/Q9%20Guideline.pdf
8. Minitab. "Example of Normal Capability Sixpack." Accessed 2 May 2022. https://support.minitab.com/en-us/minitab/20/help-and-how-to/quality-and-process-improvement/capability-analysis/how-to/capability-sixpack/normal-capability-sixpack/before-you-start/example/
9. Haas, C. N., and P. A. Scheff. "Estimation of Averages in Truncated Samples." *Environmental Science and Technology* 24, no. 6 (1990):912–9. doi:10.1021/es00076a021

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