SCALING YOUR CAR-T OPERATION: A GUIDE FOR THE LIFE SCIENCES LEADER

INTRODUCTION

SCALING YOUR CAR-T OPERATION: A GUIDE FOR THE LIFE SCIENCES LEADER

Add Value by Engaging a Facility and Technology Expert Early in Your Process

I am excited to present to you our eBook, "Scaling Your CAR-T Operation: A Guide for the Life Sciences Leader." In the rapidly evolving landscape of cellular therapies, the need to adapt and expand your CAR-T operation efficiently and effectively has never been more critical. With new CAR-T therapies anticipated to be approved within the next year, many CDMOs and CDOs need help scaling their process to a commercial level. In fact, there are approximately 300 companies that are producing CAR-T therapies or are in the early research stage. Our scientists, architects, engineers, and regulatory experts at IPS-Integrated Project Services understand the unique challenges you face and have direct experience assisting clients like you in overcoming them.

As pioneers in the field, we also understand the deep-seated aspirations that drive you. The CAR-T revolution has set in motion a seismic shift, empowering us to combat previously incurable diseases at their very core. These therapies harness the body's own immune system, reprogramming it to wage a precise and personalized war against cancer and other devastating conditions. Imagine the immense possibilities that unfold when we empower the cells within us to serve as warriors, battling disease with a ferocity unparalleled in medical history.

By investing in this eBook, you are taking a significant step toward unlocking your CAR-T operation's full potential. It is a testament to our shared commitment to advancing the frontiers of science and elevating patient care to unprecedented heights. Our visionary approach, tailored specifically to the operation of these therapies, will guide you toward transformative success. Within these pages, you will find practical knowledge gained from hands-on experience, checklists that will help guide you through the process, and specific scientific and regulatory information related to this operation.

We know that scaling up a CAR-T operation brings with it complex operational considerations and potential pitfalls. Our eBook will empower you to make informed decisions and avoid costly mistakes. By engaging a facility and technology expert early in your process, you can proactively address scalability challenges, streamlining your operations and ensuring seamless expansion as you meet the rising demands of the market. We understand the fear of getting stuck with a process that won't scale.

We also recognize that speed to market is paramount in getting your operation ready to meet the growing demand for CAR-T therapies. Time is of the essence, and every moment lost can equate to missed opportunities and potential setbacks. Because CAR-T is a new therapeutic area, it's very easy to get lost in fundraising and regulatory approvals. By working with the right partner early in your process, you can optimize your early-phase trials, ensure a competitive edge, and lower costs of production. Without a well-planned and robust supply chain strategy, even the most advanced CAR-T therapies can face significant delays and roadblocks.

At IPS, we are committed to supporting life sciences leaders like you in overcoming the unique challenges of scaling CAR-T operations. Our team can shape the entire process, end-to-end, including designing, building, and validating your scaled operation. This means assisting with proper site selection, ensuring that equipment is correct and FDA compliant, and from a construction standpoint getting you to market faster.

Together, let us forge ahead and lead the way in CAR-T operations, revolutionizing patient care and shaping the future of the life sciences landscape.

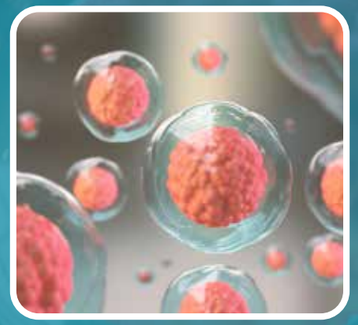
Sincerely,

TOM PIOMBINO *MANAGING DIRECTOR, AMERICAS*

ips CarTon™ Operational Readiness

CarTon™ is the end-to-end integrated compliance solution that turns medical brilliance into an operational facility. Along with iCON™, CarTon is IPS' latest solution to bring an ATMP manufacturing facility to complete operational readiness.

Where speed to market is critical for saving lives, our solution simplifies the complex maze of activities required to bring a new cell and gene therapy facility to a fully operational state. CarTon contains the entire process life cycle including facility and process requirements, standardized protocol templates, QMS/SOP development, training, and other necessities for CGMP manufacturing in a global market.



Quality by Design - CGMP Compliant Facility

- Manufacturing and Contamination Control Strategy
- Product Definition (CQAs) and Process Design (CPPs)
- User Requirements
- CGMP Facility Design Reviews and DQ
- Quality and Regulatory Approval Strategy
- Risk Assessments (ICH Q9)
- Validation Strategy (VMP)
- Life Cycle Documentation Requirements

Commissioning, Qualification and Validation

- Engineering Turnover Packages and Document Control
- Start-up and Construction QA
- Commissioning
- Facilities, Systems and Equipment Qualification
- Airflow Visualization Studies
- Environmental Monitoring Performance Qualification
- Media Fills and Aseptic Process Simulations
- Computer System Validation and Data Integrity
- Process and Cleaning Validation
- Sterilization Validation
- QC and Analytical Methods Transfer and Validation

Manufacturing Readiness and Quality Management Systems

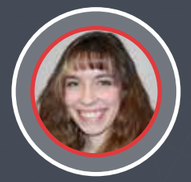
- Program and Project Management
- Quality Management System (QMS) Development
- Tech Transfer and Scale-up
- Pre-Approval Inspection Readiness
- CGMP and Internal Audit Program
- Materials and Information Management Systems (ERP/LIMS)
- Supplier Audits, Vendor Management and Quality Agreements
- Operation and Maintenance SOPs
- Recruiting, Staffing and Training
- Calibration and PM Program Development
- Cleaning, Disinfection and EM Strategy
- Continuous Improvement Program

ABOUT THE AUTHORS

TOM PIOMBINO *MANAGING DIRECTOR, AMERICAS*

Mr. Piombino has worked in almost every facet of integrated biopharmaceutical design and construction over the last 30 years. As an estimator, project engineer, and project manager, he ran preconstruction and construction projects early in his career before moving into architecture and engineering. Tom has led many projects as the process architect, project manager/director, and engineer in multiple disciplines - process, mechanical, and HVAC. As a subject matter expert, he has a deep manufacturing understanding of biologics, vaccines, cell therapies, and gene therapies. Tom finds deep satisfaction in the life sciences mission and uses his creativity and innovation to convert an abstract idea into something tangible. The breadth of his applied experience allows him to deliver valuable consultation to customers on a broad range of strategic topics, including building and optimizing businesses, real estate, risk management, board advisory, presentations, process architecture, capital planning/estimating, process modeling, marketing/sales, and facility evaluation/feasibility.

As a managing director, Tom oversees the design, construction, and compliance operation of IPS Life Sciences throughout the US and Canada.



JULIA YEARWOOD *ENGINEER, PROCESS*

Ms. Yearwood has over six years of experience within the pharmaceutical industry. Julia has experience in both lab and full-scale processes, including work with patient cells, raw materials and waste, and mRNA technologies. Julia has been involved in all project stages, from concept through construction assist, and in several roles, including system owner and overall process lead. Working on global projects, she has designed systems for the breadth of single-use facilities to vaccine continuous manufacturing plants. She takes great pride in her work on a COVID-19 vaccine project, honored to be a part of the answer to the urgent global need. Julia has performed as the process lead and contributed her work to FOYA-winning CAR-T facility projects. She works meticulously on all deliverables and is adept at communication and coordination. Julia loves knowing her work can help improve lives. She loves to be creative in her spare time — her biggest hobby is constructing and sewing costumes with her sister.

AARON WEINSTEIN *SENIOR DIRECTOR, COMPLIANCE CONSULTING*

Mr. Weinstein possesses more than 20 years of API and biotech CQV execution, project leadership and project management experience in commissioning, qualification, and validation related to state-of-the-art biopharmaceutical development and manufacturing facilities. His experience includes the development and implementation of both short- and long-term commissioning, qualification, and validation programs for projects valued up to $250 million. Aaron has provided technical and compliance consulting services, developed CQV master plans, conducted CGMP audits, CFR 21 Part 11 assessments and implemented CQV project planning and execution strategies for a number of US and multinational companies around the world.

BRIAN PEASLEY *SENIOR DIRECTOR - EMEA*

Mr. Peasley has over 25 years of experience in the biotechnology and pharmaceutical industries working for corporate, institutional, and academic clients. Brian's areas of expertise include project management and project engineering from early phases through construction and CQV. He has a strong technical background in biocontainment, HVAC, and mechanical system design for science and technology facilities. His experience and understanding of laboratory design, utility system engineering and design, utility usage profiles, and energy optimization/conservation allow him to successfully estimate engineering and design costs, establish realistic schedules, and develop successful approaches. Brian's most recent works include running large capital investment projects in the early phases for large corporate biopharmaceuticals looking to expand or improve their European operations. Brian has been married for 18 years with two children. Hobbies include donating golf balls to various ponds, forests, and streams.

GEORGE TODOROV *SENIOR PROCESS SPECIALIST, CELL & GENE THERAPY PROCESS SME*

Mr. Todorov has over 10 years of industry experience with early to late-stage process development, IND-enabling studies, supporting external partnerships, and consulting in the cell therapy and AAV gene therapy space. Before joining IPS, he directed a process group developing novel AAV manufacturing and analytical platforms through the evaluation of new technologies and continuous process improvement projects. George developed and implemented an AAV process scale-up for transient expression systems in mammalian cells, leveraging DOE yield optimization studies. His hands-on and consulting experience includes designing and coordinating laboratory expansions and GMP facilities for various cell therapy and AAV process scale-up operations. George is a meticulous, inquisitive, and data-driven leader focused on empowering and developing teams and organizations. In his spare time, George enjoys sailing, biking, and brewing. He is also the winner of the 2018 ACS Santa Clara, CA Homebrewer Competition.

CONTENTS

PATIENTS ARE WAITING: PARTNERING FOR LARGE-SCALE CAR-T FACILITY BUILDS

By Tom Piombino, Managing Director, Americas

"Patients are waiting," a phrase used by Paul Janssen, succinctly focuses on the importance of what we do and why we do it. These patients are our friends, family, and members of our communities that we care about deeply.

When it comes to difficult-to-treat cancers, the cell therapies pioneered in recent years to offer more targeted treatments have emerged as game changers for certain rare and intractable malignancies. Some of the most promising modalities in the space today are CAR-T therapies, T cells that have been modified to produce chimeric antigen receptors (CARs) on their surface, allowing them to target specific antigens on cancer cells.

As more and more CAR-T therapies achieve commercial success, the current scarcity of specialized manufacturing capacity will only serve to stall production scale-up for these crucial modalities. For many of the companies pursuing these therapies, broader indications and larger patient populations will require them to construct manufacturing facilities to meet unprecedented demand. Furthermore, because these therapies are manufactured autologously, understanding the space, staffing, containment, GMPs, and quality control considerations necessary to achieving a successful large-scale operation can be a complex undertaking.

Finding a creative partner that comprehensively can shape the design, build, and validation of a CAR-T manufacturing facility can help companies avoid costly operational missteps and leverage consolidated, diverse expertise from a single source. The result is a facility positioned to produce therapies quickly and compliantly, at volumes necessary to meet the growing and evolving needs of the patient populations these modalities reach.

IMPROVING SCALABILITY WITH A MODULAR APPROACH

CAR-T therapies are a significant and growing segment of the overall T cell therapy market, making up more than a quarter of all T cell treatments available today. This number is only projected to rise to meet the growing incidence of cancer globally, bolstered by a more widespread push to validate the efficacy of these drugs, enabling greater data access and strengthening the overall pipeline in the future. As new CAR-T therapies move through the pipeline and others launch trials for approvals as second-line therapies, the companies behind these innovative drugs must consider expanding their operations to accommodate the hundreds, thousands, or tens of thousands of doses an indication might demand.

Making the transition from producing a handful of batches using processes developed by a university or CRO to meet commercial demand requires partnering for the right design, build, and qualification expertise. IPS-Integrated Project Services (IPS), a global engineering and consulting firm specializing in highly technical facilities across the life sciences industry, has established an integrated design-build platform that leverages cross-sectional expertise to solve problems and anticipate challenges. Its experiential-based or

chain-of-custody approach has already been applied to a successful CAR-T therapy that has been scaled to produce thousands of doses per year.

In the smaller patient populations that CAR-T therapies have previously served, the bench-scale processes that work for early development — one or two people performing every unit operation, from cell harvest and activation to modification, expansion, and isolation, in a single room — have been sufficient to produce the relatively low number of doses required. But as demand for these therapies increases, this approach creates inefficiencies that can slow production or create gaps if even one technician or piece of equipment is unavailable. To address this, IPS established its chain-of-custody approach, breaking up 10- or 15-unit operations into four or five specialties, with teams focused on just a handful of core unit operations. While limiting a team's breadth of skills is counterintuitive in modern biologics-based workforce applications, this approach in CAR-T applications creates a staggered production paradigm, allowing these specialized teams to work in tandem to produce doses in rapid succession. Coupled with the right available equipment and a facility space designed to support an application's specific needs, this segmentation has already proven successful in supporting CAR-T development through Phase 3 trials and into commercial production.

ITERATING AND INNOVATING TO LOWER COSTS AND BOOST PRODUCTION

Through its prior experience in CAR-T production, IPS has iterated on its approaches to further streamline costs and timetables. Rather than utilize costly all-in-one (AIO) technologies for every part of the process, IPS positions this AIO equipment for specific unit operations and uses less expensive technologies in order to limit the number of high-cost consumables and expand operations without unduly impacting COGS. Likewise, by leveraging specialists whose entire function within the manufacturing process is two or three discrete unit operations, organizations can work on more batches at a time, achieve greater consistency, and, most importantly, reduce failure rates. This is especially critical in a paradigm where as many as one in 10 CAR-T therapies fail in production. Finally, IPS continues to find ways to both close processes at every phase of its production and reduce the background classification of the manufacturing environment where possible.

Ultimately, producing CAR-T therapies is still a labor-intensive process — IPS estimates that organizations should anticipate needing one operator for every three batches they intend to produce at a given time. Other challenges, like fomenting an adequate quality control strategy, hiring and training sufficient personnel, and instituting a serialization platform capable of tracking patient doses accurately and consistently, require companies to consider every need of their final manufacturing process as early as possible. Doing so with a partner that can integrate those variables into a facility, advise on equipment and supply chain considerations, and plan for warehousing, raw materials handling, and other factors can help better position companies to meet demand and reach more patients faster.

CAR-T FACILITY DESIGN, START-UP, AND CQV

Aaron Weinstein is the Senior Director, Compliance Consulting, IPS-Integrated Project Services. He has over 24 years of experience in commissioning, qualification, and validation within the pharmaceutical and biotech industries. Watch this video as Aaron kicks off INTERPHEX Live with his session, "**CAR-T Facility Design, Start-up, and CQV.**" Alongside industry experts on the panel, Aaron shares insights on the challenges in space planning, utilities, process equipment, and automation of manufacturing facilities that you need to know about.

Scan the QR to watch now.

ACHIEVE FLEXIBLE, OPTIMIZED MANUFACTURING CAPACITY FOR CAR-T THERAPIES

By Julia Yearwood, Engineer, Process

In the cell and gene therapy space, the complexity of the production of many of these advanced therapies requires manufacturing solutions that optimize space utilization, workflows, and supply chain management. For CAR-T therapies in particular, this equation is fraught with considerations that can, when not addressed early and comprehensively, inflate costs and undermine production volume and success rates.

As more CAR-T therapies are introduced to the market to treat increasing types of illness, the need for new facilities to accommodate this demand will likely surge in the next several years. This reality can create significant bottlenecks, as many of the CROs and CDMOs that companies may partner with for smaller scales need more capacity, resources, and expertise to ratchet up production of these drugs up quickly or seamlessly. As a result, most companies looking to produce hundreds or thousands of doses of CAR-T treatments per year will need to construct dedicated facilities designed with their treatment in mind.

PURSUING COMPREHENSIVE, COLLABORATIVE FACILITY DESIGN TO SUPPORT GROWTH

Although the fundamental processes and technologies supporting CAR-T production are essentially universal, the diversity of these products can necessitate a closer look at a facility's overall design. For example, certain live viruses required in the production of CAR-T treatments that are difficult to procure in larger quantities may force companies to consider dedicating a portion of their facility to producing that virus. Likewise, because most CAR-T therapies are produced autologously, understanding the precise equipment and space needed to support safe, adequate production requires careful up-front planning that can be replicated as an operation scales further.

A CAR-T manufacturing process is also likely to change, even as a facility is being constructed, due to technological changes or production demands. Balancing existing variables with the potential for new needs is crucial; ultimately, identifying a design-build partnership that can offer companies flexibility in the face of these evolving considerations is vital to a successfully executed facility. As evidenced by the COVID-19 pandemic, externalities such as supply chains can shift quickly, and planning a facility around this potential, at least for core raw materials, may help organizations remain flexible in the face of supply constraints.

Our teams engage in ongoing personnel flow and layout reviews to ensure a proposed facility is optimized for multiple steps and operating units across dozens or hundreds of personnel. This is especially important as a CAR-T application scales. Transitioning from the same handful of people performing the entire process to a more segmented, staggered, chain-of-custody approach to facilitate more batches means designing to support that phased production at the outset. Likewise, our experts can offer creative solutions for challenges related to warehousing, storage, containment, or other

design variables. For example, we have worked to upgrade a client's existing cryogenic storage method from freezers filled with liquid nitrogen dewars to a liquid nitrogen distribution system designed to feed controlled rate freezers, maintained by supporting utilities engineered-to-purpose. By optimizing air and gas distribution as part of the facility design, IPS helps clients balance the cost of supporting bulk materials for a facility and their asset's projected market share.

This kind of utility optimization is one of IPS' key offerings, alongside a robust equipment supply chain portfolio, longstanding incumbent expertise, and accessible, flexible consulting services to support a project from start to finish. Being able to anticipate and advise on the equipment needs of a project throughout its life cycle, as well as help organizations forecast for potential contingencies that may require new designs, are critical elements of this approach. Additionally, the highly manual small-batch processes that typify the CAR-T proces often require unique approaches to facility design and utility integration to accommodate the larger numbers of personnel and process steps involved. Ideal designs enable as much automation and closed processing as possible for a given asset.

PARTNERING FOR THE FUTURE

Whether a company is planning to build a facility from scratch or rework an existing one, the nuances of its unique CAR-T asset are likely to require some innovation to achieve optimized manufacturing. Designing facilities that can be easily reconfigured or expanded to accommodate future needs — particularly around the utilities that would enable faster expansion — is an essential component of that innovation. This is crucial as the number of CAR-T therapies in the development pipeline continues to grow, mainly in response to a global cancer rate increase.

As a longstanding design-build partner in the biotechnology and pharmaceutical industries, IPS is positioned to help advanced therapy developers establish facilities optimized for the highly technical, complex workflows that CAR-T production requires. Its chain-of-custody approach to facility design, which segments the dozen or more unit operations that typify a CAR-T workflow into four or five operator specializations, can streamline a company's existing processes and enable faster, more consistent production. This segmentation, coupled with state-of-the-art equipment strategically leveraged and facility space designed to support an application's specific needs, has already proven successful in supporting CAR-T development through Phase 3 trials and into commercial production.

REPURPOSING A US-BASED LEGACY CELL THERAPY FACILITY FOR FLEXIBILITY AND EU COMPLIANCE

By George Todorov, Senior Process Specialist, Cell & Gene Therapy Process SME, and Aaron Weinstein, Senior Director, Compliance Consulting

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

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

The transition of cell and gene therapies (C&GTs) from laboratory to clinical use has been a revolution, decades in the making. ATMPs are poised to capture a significant portion of the biopharmaceutical industry, which motivated the subject company of this case study to expand its current business model to incorporate CDMO practices.

FACILITY CONVERSION DESIGN

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

ATMP OPPORTUNITIES AND CONSIDERATIONS

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

The transformative chimeric antigen receptor T cell (CAR T) therapy, for example, starts with a patient's own T cells, which are isolated from an autologous donation of blood or leukapheresis product (leukocytes or white blood cells isolated from blood). The donor blood or leukapheresis product is collected in a manufacturing

facility in a closed IV bag known as a leukopak. Then, it is shipped to a manufacturing facility where the patient's T cells are modified to produce CARs. The CAR T therapeutics specifically target and destroy cancer cells, rendering tumors vulnerable to the patient's immune system.

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

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

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

Table 1: Risk review summary.

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

AUTOLOGOUS VS. ALLOGENEIC PRODUCTS

CAR-T products fall into two different types: autologous products and allogeneic products. Understanding which products you are working with will heavily inform your facility design. Autologous products focus on a single patient and/or donor, with all products being produced specifically for that patient. Allogeneic facilities have the potential to be much more efficient by making more drug products with a smaller amount of starting materials.

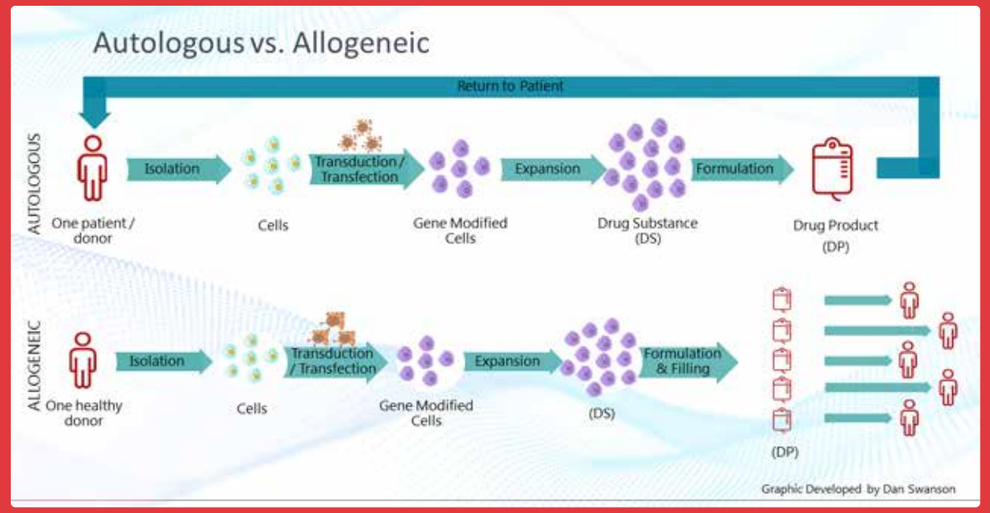


Figure 1- *Autologous vs. allogeneic cell therapy product manufacturing*

THE CHALLENGES OF COMPLIANCE WITH EUROPEAN REGULATIONS

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

Annex 1 requires manufacturers to develop a contamination control strategy to govern their manufacturing process, which may require a comprehensive reexamination of processes at a given facility.

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

Mobile lab bench configurations and modular equipment enable equipment changes to support a range of client processes using different brands of equipment platforms. The question then becomes whether the facility,

flows, engineering controls, and associated procedures can become robust enough to continuously change production while adhering to the current GMP.

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

OVERVIEW OF PROPOSED MODIFICATIONS

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

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

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

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

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

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

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

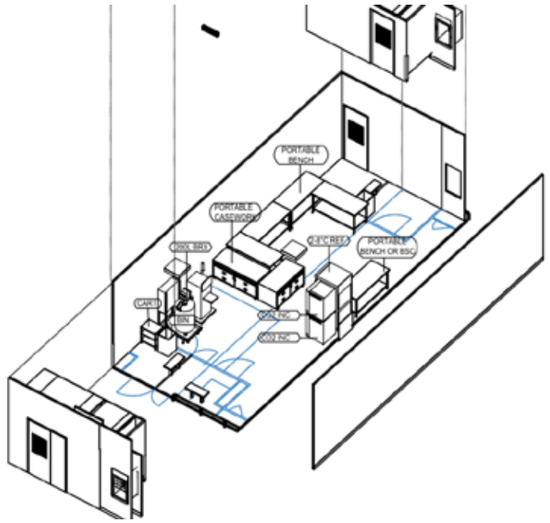


***Figure 2** - Isometric view of a single production module designed to house various open and closed process equipment ranging from bench-top systems to a 200L bioreactor.*

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

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

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

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

Additional operational considerations such as multiple shifts, media prep, and cold room storage spaces shall also be considered and modeled during future design phases. Based on the number of 200-L processes chosen for the final facility layout, automated filling and inspection equipment to support large-scale allogeneic processes must be carefully considered. Isolated filling lines can be operated in a Grade C or Grade D background, reducing the required Grade B footprint. Semi- or fully automated inspection machines can be operated in CNC areas and offer the benefits of a lower inspection footprint and lower staffing levels.

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

FACTORS FOR COMPLIANCE

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

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

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

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

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

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

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

The design basis is to allow each module to continue operating independently from other air handling unit (AHU) systems, enabling the modules to be upgraded at different times. This would require separate AHUs for each module. To meet multiproduct facility requirements for single-pass air listed in the guidelines on GMP for ATMPs, the current AHUs must be replaced with higher-capacity systems, which will also require additional modifications to utility supply lines and additional capacity to the current facility's chiller plant.

Table 2: Production module configurations considered during concept design

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

CONCLUSION

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

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

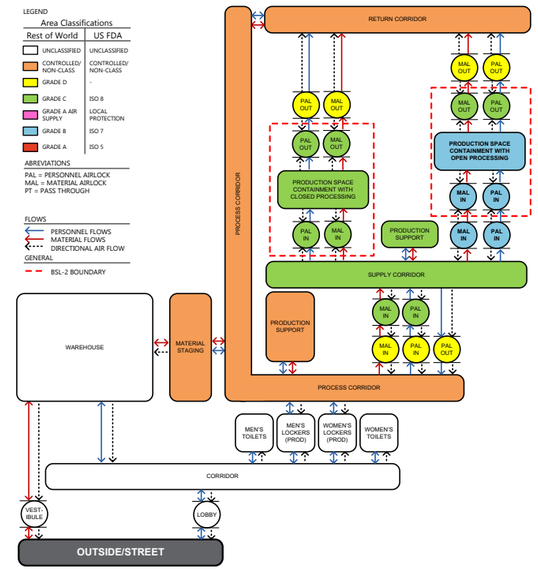


***Figure 3** - Zoning & Transition Diagram example defining GMP area classifications, stepwise transitions, operational flows, and directional airflow. It establishes the rules that the layout should follow.*

CHECKLIST FOR SCALING YOUR CAR-T OPERATION: A GUIDE FOR LIFE SCIENCES LEADERS

1 DEFINE CLEAR OBJECTIVES:

a. *Clearly outline your goals and objectives for scaling your CAR-T operation.*

b. *Identify the desired production capacity and projected growth.*

2 ENGAGE A FACILITY AND TECHNOLOGY EXPERT EARLY:

a. *Collaborate with a reputable full-service EPCMV firm specializing in pharmaceutical manufacturing.*

b. *Involve experts who understand CAR-T processes, facility design, and technology requirements.*

3 ASSESS CURRENT OPERATION:

a. *Conduct a comprehensive assessment of your existing CAR-T operation.*

b. *Evaluate facility capabilities, equipment, personnel, and regulatory compliance.*

4 IDENTIFY GAPS AND CONSTRAINTS:

a. *Identify any limitations or constraints that may hinder scaling your operation.*

b. *Determine if additional resources, equipment, or facility modifications are required.*

5 DEVELOP A SCALABILITY PLAN:

a. *Create a detailed plan that outlines the steps and timeline for scaling your operation.*

b. *Consider factors such as facility expansion, process optimization, and technology upgrades.*

6 OPTIMIZE PROCESS EFFICIENCY:

a. *Streamline CAR-T manufacturing processes to increase efficiency and reduce costs.*

b. *Implement automation, robotics, and data analytics to improve productivity.*

7 ENSURE REGULATORY COMPLIANCE:

a. *Stay up to date with regulatory requirements for CAR-T manufacturing.*

b. *Engage with experts who have experience in navigating regulatory challenges.*

8 ESTABLISH QUALITY CONTROL MEASURES:

a. *Develop robust quality control systems to ensure product safety and efficacy.*

b. *Implement rigorous testing, monitoring, and documentation processes.*

9 TRAIN AND DEVELOP STAFF:

a. *Invest in training programs to enhance the skills and knowledge of your workforce.*

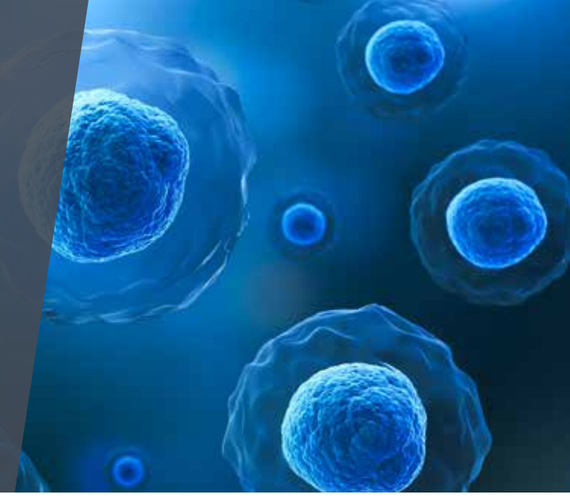
b. *Foster a culture of continuous learning and development.*

10 MONITOR AND EVALUATE PERFORMANCE:

a. *Continuously monitor and assess the performance of your scaled CAR-T operation.*

b. *Collect data, analyze metrics, and make necessary adjustments for optimization.*

CELL THERAPY FACILITY DESIGN SYNOPSIS: HORIZONTAL VS. VERTICAL



By Brian Peasley, Senior Director - EMEA

There are many factors in the site selection and facility design of cell therapy facilities. As sites are evaluated, one consideration is whether the building should have a horizontal (single-story) or a vertical (multi-story) massing. This article summarizes IPS' experience and findings over the last five years of considering factors behind the vertical vs. horizontal decision.

FUNCTIONAL SPACES AND SCALE-OUT

There is a natural fit for stacking operations like buffer and media preparation above cell culture in large-scale stainless-steel biotech facilities. In cell therapy facilities, there isn't a process or material movement driver for vertical configuration. At the same time, long travel distances in a single-story facility could not be fit for function depending on what material and when in the process it is traversing that distance. Mapping out the movements within the process with allowable time durations can help determine what functions need to be adjacent to each other and where logical breaking points are in the process. For example, after formulation with dimethyl sulfoxide (DMSO), there is a time-critical need to fill and freeze the product grouping those functions. Some breakpoints are clear; for instance, moving frozen apheresis materials from receiving to cell selection can take as long as the CryoPod can hold temperature. Other breakpoints that initially may not have been characterized may have to be considered due to space or distance concerns, such as, for example, evaluating how long the product can stay at ambient conditions between cell expansion and formulation. The concept of mapping out movements is important for fitting within a smaller footprint of a multi-story building, as well as the scale-out of horizontal facilities.

We ask our clients what makes the most sense for their facilities, i.e., traversing the full length of the building to get to the freezers or shortening the distance with replication of a freezing area.

LOCATION. LOCATION. LOCATION.

We have heard it before, the common phrase for buying and selling real estate. Sometimes we need to step back and recognize that building a cell therapy facility is a real estate transaction. Buying property, leasing space, or repurposing an existing facility sets a fundamental basis for the facility's design and ultimate function. Some questions to consider when evaluating a location include:

- Does the location offer access to personnel with the right talents to staff the facility?
- Is co-location with R&D needed for ease of technology transfer and continued process development?
- Are there other company functions that should be co-located for business reasons?
- How does the location work for the logistics of vein-to-vein delivery?
- Is there a financial incentive (lower-cost space, government funding, tax breaks, recoveries on depreciated assets)?

In one case, a company chose a vertically oriented facility for an ATMP program that spread their operations across multiple floors. The small footprint of each floor made process transitions less than ideal. However, the financial support from the local city government drove the selection of the site and its planned use of an existing vertical facility. There are many instances where government support doesn't always drive massing based on the site. For instance, another facility IPS completed followed a horizontal approach to allow for multiple small independent suites to receive government funding as a startup incubator space.

PROJECT DELIVERY

As we think about space, we need to consider the timeline and allocated capital. Many of the cell therapy products are racing to commercial launch, driving us to look at existing buildings. These buildings can vary from a high-rise medical building in an urban center or a shell building originally intended to be a warehouse. One facility IPS completed was a renovation of an idled packaging facility. Getting into an existing shell was one of the key factors allowing the project to go from concept to fully installed in 11 months.

Speed to market is especially important in the cell therapy space, but it should not be the singular focus. For example, another consideration might be master planning for scale-out/up for long-term production needs. Horizontal facilities can provide a straightforward expansion using a mirroring approach or adding modules. A modular cleanroom system is another consideration when rapid builds are needed. While modular cleanrooms have been successfully used in vertical facilities, there can be additional design challenges due to available free height. These challenges don't disappear with traditional cleanroom construction. However, the time to design and build adaptive solutions can lead to a slower and more costly delivery than equivalent space in a horizontal facility.

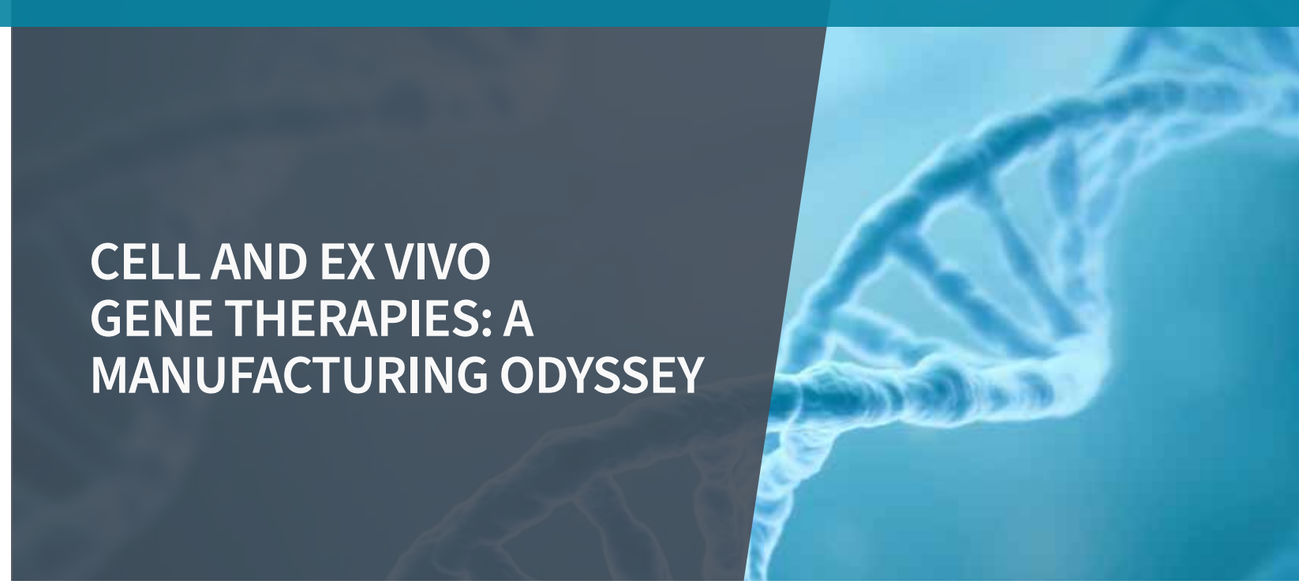
DETERMINING THE RIGHT SOLUTION

Choosing between a vertically- and horizontally-oriented site can be challenging because we are often forced to prioritize one requirement over another. In one further IPS example, a company started with an initial design to renovate space in a high-rise medical building they occupied in a downtown US city. The advantage of this approach was the proximity between manufacturing and the company's researchers and clinical trial participants. However, the disadvantage was that the cost and complexity of the renovation outweighed the advantages of proximity. Based on the business case analysis, it was determined to design an expansion at a CMO's single-story (horizontal) facility outside of the city to accommodate the increased demand.

Finding the right approach for your next cell therapy facility can be distilled into the following:

- Horizontal designs:
  - Straightforward scale-out
  - Lower first cost
- Vertical designs:
  - More efficient use of land
  - Proximity to talent pool and resources
  - Opportunity to build in other company functions
  - Purposeful separation of operations by floor needed
- Other out (horizontal) vs. up (vertical) drivers:
  - Existing assets
  - Available real estate
  - Local land-use regulations
  - Proximity to supply chain (particularly autologous)

There isn't a universal "one solution fits all" answer to which direction is the best. Finding the right partner to help you navigate through options to determine whether going up or out is a valuable next step to finding the right solution, driven by several factors that are unique to your needs.



CELL AND EX VIVO GENE THERAPIES: A MANUFACTURING ODYSSEY

By George Todorov, Senior Process Specialist, Cell & Gene Therapy Process SME

In recent years, ex vivo gene therapies have stirred hope for a curative treatment for B cell malignancies and, in the future, solid tumors. Somatic cell therapies have also been shown to be effective against metastatic prostate cancer and in hematopoietic or immunologic reconstitution therapies.

CAR-T, CAR-NK, and T cell receptor (TCR)-T cell therapies are generated by administering recombinant genetic material that alters the properties of living cells. Genetic alteration of the cells is performed outside the body before the cells are delivered to the patient, so these therapies are classified as ex vivo gene therapies. In contrast, somatic cell therapies are human cells transplanted to repair damaged tissue or cells, and include modalities such as hematopoietic or mesenchymal stem cells and cellular immunotherapies.

Both ex vivo gene therapies and somatic cell therapies have seen clinical success and commercial licensure. Cell immunotherapy products such as CreaVax RCC and Immuncell-LC have been licensed in South Korea since 2007. Dating back to the early 2010s, Dendreon's Provenge was among the first somatic cell therapies to receive FDA and EMA approval. However, CAR-T cell therapies have taken longer to reach commercialization. Yescarta and Kymriah secured FDA approval in 2018, paving the way for others, such as Tecartus, Breyanzi, and Abecma.

Ex vivo gene therapies and somatic cell therapies come in two flavors: autologous and allogeneic. Autologous cell and ex vivo gene therapies are often considered a safer approach than allogeneic equivalents because there is no risk of graft versus host disease. CAR-T therapies were originally established as autologous products with the need to "scale out" the manufacturing processes to serve a growing market. However, scaling out presents major manufacturing and economic challenges at the commercial level, which has led developers to heavily invest in allogeneic modalities. Allogeneic products can enable scale up of manufacturing processes and "off-the-shelf" solutions that will treat large patient populations, while also lowering cost and reducing manufacturing and supply chain complexity.

PLANNING FOR THE FUTURE

With the number of cell and ex vivo gene therapy products entering the clinic growing exponentially, we must, as an industry, look ahead and plan accordingly so that we can deliver these revolutionary medicines to large patient populations safely and efficiently. Regardless of the specific modality – and the autologous or allogeneic format – cell therapy

processes are not standardized and there is significant room for evolution. A number of serious questions remain unanswered:

- How does one efficiently scale out or scale up autologous and allogeneic manufacturing processes to meet growing demand?
- How can an inherently open manual process be converted to a closed and semi or fully automated process?
- What does the evolving regulatory landscape for cell and ex vivo gene therapies push us to anticipate when designing a manufacturing process?
- What do we, as an industry, need to consider when planning to manufacture multiple patient lots and/or multiple cell therapy products under the same roof?
- How can the cost of manufacturing be lowered to make these life-saving therapies more accessible?

THE AUTOLOGOUS WAY

The autologous cell therapy industry has rapidly embraced single-use technology and closed processing for GMP manufacturing, but currently available formats for cell processing present logistical challenges for high capacity multi-product and/or multi-client manufacturing. Equipment developers have in recent years provided two contrasting approaches for closed processing of autologous therapies:

- Modular, single-use equipment that addresses the need of individual processing steps or stages (apheresis, cell isolation, engineering, expansion, and harvest/formulation).
- End-to-end equipment with single-use consumables that encapsulates the entire process, following apheresis, in a single instrument.

The hype around CAR-T cell therapies has spurred bioprocess equipment manufacturers into a competitive race to offer modular instrumentation. The result? Plenty of choice for manufacturers. Terumo, Thermo Fisher Scientific, Cytiva, Fresenius Kabi, and others now offer a variety of instruments with parallel functionality, leaving the end-user with several possible configurations and a wide range of processing strategies. Similarly, there are now multiple vendors offering end-to-end solutions in a single system, including Miltenyi, Lonza, Draper, and Cellares. Developers must carefully consider the tradeoffs between housing the process in one system versus multiple specialized instruments.

End-to-end instruments have a small footprint but this approach ties up the whole instrument for 1-2 weeks while a single batch is produced. Separate instruments, on the other hand, can have higher utilization while accommodating multiple batch processing in the same space. This is possible because not all manufacturing steps require the same amount of time to complete. For many processes, the cell expansion operation

***Figure 1** - Lonza Cocoon®*

***Figure 2** - Cellares Cell Shuttle*

requires the bulk of the manufacturing time. With separate instruments, facility footprint and capital can be dedicated to the cell expansion equipment to minimize the bottleneck, while other equipment can be limited in quantity and readily shared between batches.

Unfortunately, there is no one right answer; the best configuration is largely dependent on the drug manufacturer's capacity requirements, process duration, available cleanroom space, and manufacturing model (in-house versus CDMO). Benchtop end-to-end solutions may be a great approach for small clinical programs or quick manufacturing processes and, as throughput demands increase and plans are made for commercial scale-out, it is common to see clients adopt a hybrid approach. For example, clients may perform T cell enrichment, activation, and transduction in a Miltenyi CliniMACS Prodigy, expansion steps in wave reactors, and harvest/wash/formulation in a Cytiva Sefia or similar instrument. In this example, a low number of Prodigy and Sefia instruments are used for the front and tail ends of the process, while an army of wave reactors takes care of parallel batch expansions to increase throughput and allow for parallel processing in the same space. If hybrid and modular processing approaches for autologous manufacturing retain their utility as the industry matures, there will be a significant opportunity to weave in automation. It is also possible to envision robotic systems shuttling and manipulating batches of cells between modular instruments, which would increase efficiency and throughput, while lowering operating costs.

Adding complexity to the maze of end-to-end instrumentation, Lonza offers the Cocoon, which encapsulates the entire process in a single-use cassette format (Figure 1). It delivers similar capability to the CliniMACS Prodigy, in a much smaller footprint, and can integrate with the Lonza Nucleofector to enable electroporation. Lonza is also developing a Cocoon Tree format that enables a compact scale-out approach by packing a large number of Cocoon pods in a small space, which could be a highly effective solution for high-capacity manufacturing plants or CDMO facilities. When manipulation is required, a motorized system rotates the pods to make them accessible for the operator. Another option, expected to hit the market in 2024, is the Cellares Cell Shuttle – a fully automated end-to-end cell therapy system that uses an industrial robot to move closed cell processing cartridges between unit process operation stations from cell enrichment to formulation. However, the Cell Shuttle does not integrate a fill station, so the user must consider a separate filling solution. The system can execute over 10 workflows simultaneously and, by taking advantage of this format, developers can cue up multiple batches staggered behind one another (Figure 2).

CLOSED OR OPEN?

Today, there is an abundance of closed processing options for autologous ex vivo gene and cell therapies, all with their own pros and cons, but the majority of cell therapy programs begin R&D and process development in academia with open, manual operations in a biological safety cabinet (BSC). It is a tremendous challenge to rapidly transition a BSC process to closed systems – and the cost of single-use equipment is usually prohibitive to academic labs. However, it is critical to industrialize academic processes prior to technology transfer for GMP manufacturing to avoid program delays, improve product safety, and simplify regulatory review. To help address this gap, developers and academic institutions are investing in collaboration centers that will help bring GMP manufacturing infrastructure and equipment to cell therapy programs developed in academia.

But what about leaving the process open? Sure, this may be an unpopular idea these days, but avoiding a complete overhaul of the original BSC process can accelerate development timelines – if developers have a good approach to maintaining an aseptic environment. In recent years, isolator manufacturers have heavily invested in the ex vivo gene and cell therapy industry to bring these novel processes

***Figure 3** - Modulator Isolator Configuration*

into well-established Grade A aseptic processing environments. Companies such as ProSys, Comecer, SKAN, Harro Hofliger, OPTIMA, and their partners have delivered innovative isolator configurations that offer end-to-end processing for manual or partially automated manufacturing, and manual or fully automated filling systems for fully closed vials or cryo-bags.

Adopting isolator technology comes with significant upfront investment, which often scares away small companies. However, this knee-jerk aversion to the cost fails to consider the long-term advantages of isolators in commercial manufacturing. Adding to the advantages of operating in an aseptic environment, housing the process in an isolator can realize considerable cost savings during the facility build and operation because this approach enables manufacturing in a Grade C room rather than Grade B. An isolator system may cost several million dollars, but the annual disposable gowning cost for a single technician operating in a Grade B cleanroom can run to ~$30,000, excluding Grade B operator training, qualification, and re-qualification. One year of operation can quickly surpass the cost of an isolator when operating a cell therapy facility of ten or more Grade B suites, to a point where the isolator truly pays for itself in such settings.

Furthermore, modular isolator configurations allow for process and equipment flexibility because they can be configured and strung together with bespoke modules that can evolve with the process (see Figure 3 as an example). This type of configuration allows for independent decontamination of each module, enabling multi-product manufacturing in the same space. Operating the isolator in an assembly line fashion maximizes system utilization as batches progress through processing modules. Though several isolator providers offer similar functionality, some are taking leaps in engineering automation solutions to enable high throughput processing. For example, CO.DON AG is manufacturing their Spherox product in an automated facility featuring Comecer's FLEXYCULT mobile incubation system for docking incubators that are shuttled between isolators and a CNC area using a robotic handler running in a central spine corridor (see Figure 4). Innovations such as modular processing isolators and the FLEXYCULT enable processing of a large number of autologous batches in a small number of isolators, and allow us to dispel the notion that legacy manual processes cannot be scaled out.

It is important to note that all of the approaches to multi-product manufacturing described above are closely monitored by regulators, and are acceptable provided adequate measures are taken to prevent cross-contamination and mix-up of materials. Chain

***Figure 4** - FLEXYCULT™ System with incubator handler in CNC, courtesy of COMECER*

of identity is paramount for autologous products; hence, sponsor companies must have established and validated systems to track the donor material and engineered cells throughout each step of the process, subsequent sampling, storage, and shipment. It is only acceptable to house more than one batch or product in the same space if using closed and contained systems. Regardless of whether one uses closed single-use equipment or isolators, the EU Guide on GMP specific to ATMPs calls for 100 percent air exhaustion when using more than one viral vector for engineering ex vivo gene therapies in the same room.

ALLOGENEIC CONSIDERATIONS

While autologous therapies are often considered the faster route to securing life-saving treatment, such a generalization fails to consider the supplier's total batch capacity and the point at which batch production can actually begin. Allogeneic therapeutics can circumvent the nightmare scenario of a patient dying before an autologous batch production is complete or even initiated by providing an off-the-shelf alternative that could potentially help thousands of patients per batch. Autologous and allogeneic ex vivo gene therapies and cell therapies share many process elements, and though the cell expansion and harvest may vastly differ in scale, they have common scientific principles. These similarities present some advantages to developers and CDMOs looking to transition from autologous to allogeneic – or wanting to house both modalities under one roof. That said, here are few key differences to bear in mind:

- A healthy donor typically provides the starting material.
- Tissue typing should be carefully matched with receiving patients to avoid host rejection or the need for immunosuppression.
- Isolated immune cells or stem cells are banked prior to initiating the manufacturing process, akin to a master cell bank that is used for biologics manufacturing.
- Allogeneic cell therapies are expanded to a much larger scale.

Regardless of the therapeutic modality (CAR-T, stem cell, cellular immunotherapy), allogeneic processes require scaling up rather than scaling out – taking the early-stage process and increasing the output of product using larger equipment sizes or volumes to generate enough product to treat a larger patient population. However, these therapies are generated with primary human cells that have a finite population doubling, so the feasible culture scale-up cannot currently reach the volumes of biologics. Combining scaling up and scaling out together could be a useful approach to address limited population doubling. For example, scale up to 50 L or 200 L could then be scaled out to multiple 50 L or 200 L reactors. Culture intensification is also highly desirable to maximize the cell density of allogeneic and autologous batches, which is why some developers are using perfusion to increase the output of both modalities.

THE SCALE-UP CHALLENGE

The final fill, inspection, and labeling steps present a looming challenge to allogeneic processes as they grow in scale. After the point of DMSO (or other cryopreservative) addition, there is a narrow window of 1-2 hours during which the product must be filled, inspected, and labeled so that the cryopreservation cycle can be started in time to avoid damage to the cells. It is therefore imperative to get a head start on studying and designing these final steps to avoid costly complications during a facility design or late stage clinical studies. Automated vial filler providers, such as Aseptic Technologies and Flexicon, offer sophisticated and customizable systems that can be integrated into isolators to maintain an aseptic environment (see Figure 5A). Processes terminating in a bag fill rather than vials can also be automated and scaled. Innovators such as Single Use Support now provide aseptic filling systems that feature a single-use disposable fluid path and can simultaneously fill multiple single-use bags to accommodate a wide range of batch sizes (see Figure 5B). Selecting an isolator and/or automated filler are important steps, but they must not be done in a vacuum. Understanding the throughput requirement, batch size and timing of filled vial nests or batches of bags exiting the filling chamber is critical to informing the strategy for labeling and inspection.

Figure 6 - Crystal® L1 robotic vial fill line (top) and Single Use Support ROSS.FILL CGT bag filler (bottom)

Manual inspection is time-consuming and, as batch sizes increase, one must plan for multiple inspection stations, adequate space, and enough personnel. Semi-automated or automated inspection solutions are available from various suppliers, including Korber Pharma, Antares Vision, and Brevetti. This kind of instrumentation was originally designed for large-scale pharmaceutical inspection; however, scaled down versions are now available to serve the cell and gene therapy industry. Analogous to the isolator paradigm discussed above, automated inspection equipment is a costly investment but can decrease processing time, staffing needs, gowning costs, and the required cleanroom footprint. Also, keep in mind the fact that manual or automated visual inspection must satisfy USP 788, 790 and 1790 guidelines, and implementing automated inspection requires lengthy validation studies that must be executed at the manufacturing site.

Last but not least, labeling can be manual or automated, but both the timing and location for this operation must be considered. Labeling is typically done in a Grade D or CNC environment, but some cell therapy developers consider performing this function in the filling suite to avoid wasting valuable time in moving the product to another area ahead of cryopreservation. Performing labeling in the filling suite raises the concern of introducing particulates in a Grade C environment and one must properly package and sanitize incoming labels, but alternative strategies are now available, such as laser-etching QR codes and product information on the vials prior to the fill or applying pre-printed label sleeves following cryopreservation, to alleviate the fill/finish timing constraint.

THE ROAD AHEAD

Autologous and allogeneic ex vivo gene therapies have significant process overlap, including cell isolation, activation, engineering, initial expansion, formulation, and the need for cold chain. For example, cell isolation, activation, and expansion procedures take advantage of antibody-conjugated paramagnetic beads to capture the correct cell type or mimic interactions that trigger activation and cell expansion. A magnetic field is applied to isolate cells that will be engineered into autologous or allogeneic products, or to remove magnetic beads from the culture after processing. Biodegradable paramagnetic beads are also readily available and developers must weigh the benefits of eliminating the de-beading step against the results obtained with different bead products and the risk of introducing residual impurities.

Engineering ex vivo gene therapies to express a CAR gene is predominantly carried out by transduction with a lentivirus or other retroviral vector. Viral transduction is completely expandable to allogeneic process scales, but one must consider that retroviruses are typically handled in BSL2 environments, which require proper measures and facility design for biocontainment and segregation. Aside from the safety concern, the cost and timeframe required to produce GMP-grade viral vectors are significant so it's worth considering alternative options. Electroporation methods use an electric field which temporarily permeabilizes the cell membrane, allowing for uptake of DNA into the cell. This technology started out as a cuvette-based benchtop format but has expanded into a scalable single use format offered by companies such as MaxCyte and Lonza, enabling its use in large scale allogeneic processes. As the industry continues to mature, expect to see wider adoption of electroporation instrumentation in cell therapy and viral vector manufacturing.

Looking toward the future of these life-saving therapies, raw material suppliers, equipment manufacturers, architecture and engineering firms, and drug developers all need to coordinate efforts aimed at reducing manufacturing cost and expediting delivery to patients in dire need. Process closure, end-end solutions, automation, and declassifying manufacturing space are all strides in the right direction on our journey to make these therapies more accessible. To add more manufacturing capacity, the industry is looking beyond scaling out autologous and scaling up allogeneic processes. But one can envision a future where equipment innovators and regulators come together to enable decentralized end-end bedside autologous cell therapy manufacturing across a wider network of hospital environments.

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KNOWLEDGE, SKILL & PASSION

ABOUT IPS-INTEGRATED PROJECT SERVICES

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