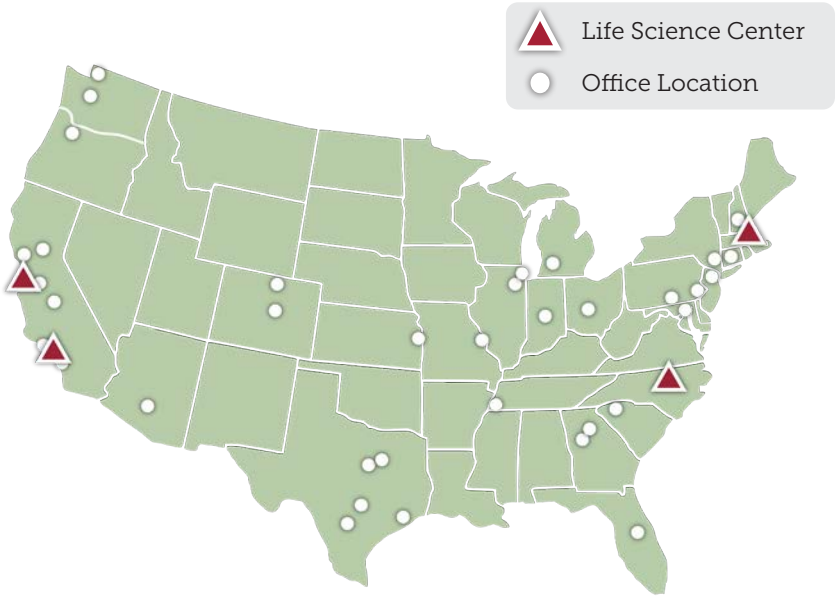
Design Group

Cell & Gene Therapy Capabilities and Design Guide

We Are Design Group

Design Group operates from 45+ offices in the United States providing engineering, consulting, and technical services to the world's leading companies in the Life Sciences, Advanced Technology, Industrial, Food & Beverage, and other market sectors. Our nearly 1,500 technical and engineering professionals have direct industry experience in facility and process engineering, architecture, construction management, process automation, control system integration, regulatory compliance, enterprise technology, and other consulting services.



Design Group Life Science Professionals provide engineering and construction leadership for Cell and Gene Therapy, Biotechnology, Pharmaceutical, and Medical Device clients from offices across the country. Design Group has completed over $1 Billion in Engineering, Procurement, Construction Management, and Validation (EPCMV) projects.

Market Sectors

Cell & Gene Therapy	Medical Device
Biotechnology	Regenerative Medicine
Pharmaceutical	

Our Capabilities

Architecture & Engineering

Design Group's process-driven architectural and engineering services integrate evolving regulatory guidance into facility design by incorporating industry standards to optimize manufacturing capacity, process flow, and space utilization.

- Architecture & Engineering
- Facility Planning
- Facility Condition Assessment
- Land Planning
- Building Information Modeling
- Process Design
- Process Development
- Process Automation
- Wastewater Solutions

Control System Integration

Design Group is one of the largest System Integrators in the US, providing automation and CSI services.

- Electrical Design
- Control Panels
- PCS/EMS Integration
- Process Controls
- Information Solutions
- Machine Safety
- Data Integrity & Analytics
- Network Assessment
- Electronic Batch Records

Regulatory Compliance

Design Group is a leading supplier of validation, quality engineering, and regulatory consulting services.

- Commissioning & Qualification
- Computer System Validation
- Process Validation
- Cleaning Validation
- Quality Compliance
- Regulatory Services
- Supplier Qualification Audits & Inspection
- Audit Readiness

Construction Management

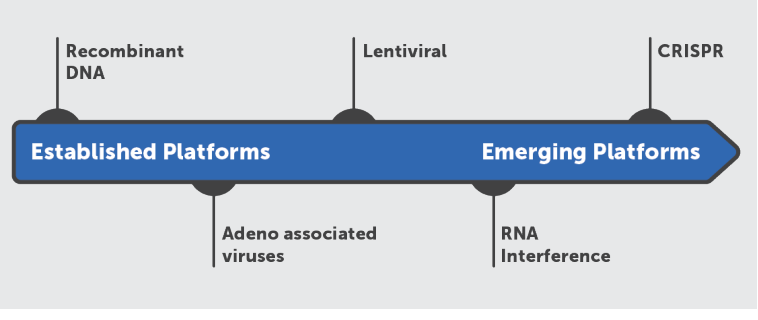
Design Group develops integrated solutions from concept design through construction documents using our full-service, in-house construction management team.

- Pre-Construction
- Construction
- Facility Commissioning

Cell & Gene Therapy Overview

In recent years, the industry has experienced exponential growth in the number of investigational new drug (IND) applications for clinical studies pertaining to Cell and Gene Therapies. Subsequently, the FDA continues to publish guidance documents for Cell and Gene Therapy clinical development and manufacturing.

The personalized immunotherapy offered by currently approved and late stage clinical Cell and Gene Therapy technologies presents the challenge of scaling manufacturing processes horizontally rather than vertically, as is typical of traditional biologics. This creates a unique set of challenges for facility design to ensure the appropriate engineering control, material and personnel flows, and system architecture requirements are met.



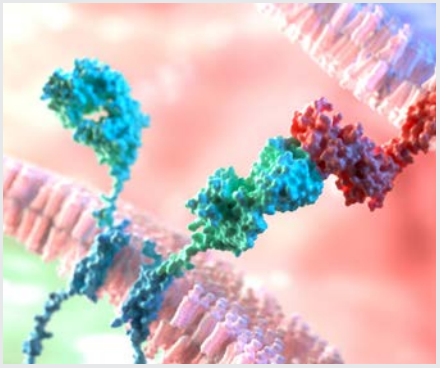
Design Group's multi-discipline engineering, quality, and validation professionals understand the unique set of challenges for facility design to ensure the appropriate containment strategy, cleanroom design, equipment configurations, and system design requirements are achieved to support Cell and Gene Therapy clinical and commercial manufacturing.

CONCEPT TO REALITY: PRODUCT LIFECYCLE MANAGEMENT

Design Group leverages several 3D design software platforms to optimize multidiscipline engineering design to execute successfully projects throughout their lifecycle, from concept to occupancy. Beginning with a laser scan capturing existing conditions, facility and equipment are modeled for layout, presentation to our clients, and use in the preparation of all project documentation.

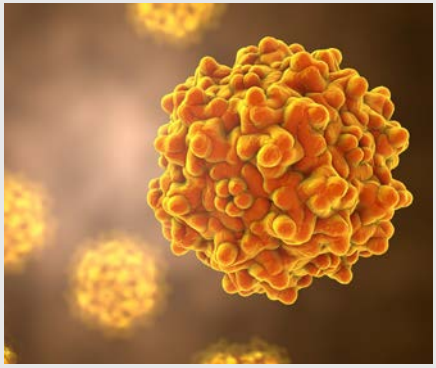
Cell & Gene Therapy Overview

Design Group has partnered with leading Cell and Gene Therapy clients in design, permitting, construction and validation to implement ISO classified environments and laboratory functions to allow our clients to produce CAR-T, X-SCID, and viral vector therapies.



CAR-T

Autologous CAR-T (chimeric antigen receptor T-cell) therapies engineer T-cells from a patient's blood to express a chimeric antigen receptor to recognize a specific protein or antigen on a tumor cell and attack the tumor. Allogenic CAR-T therapies begin with donor material that is manufactured for the treatment of different patients.



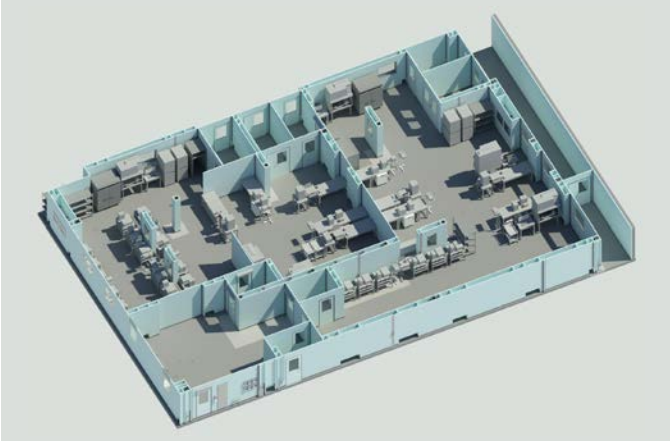
VIRAL VECTOR

Viral vectors are used to introduce genetic material into the nucleus of the patient's cells. There are three primary types of viral vectors: adenoviral vectors, adeno-associated viral vectors (AAV), and lentiviral vectors. AAV are small viruses with a mild immune response that cannot replicate without external factors making them a prime candidate for use as a viral vector.

CRISPR/CAS9

CRISPR/Cas9 is a gene editing technique that can target DNA sequences for modification using a specialty designed gRNA (guide RNA) molecule. CRISPR/Cas9 can be used to modify T-cells for CAR-T therapies and is currently being investigated for ex vivo and in vivo cell therapies.

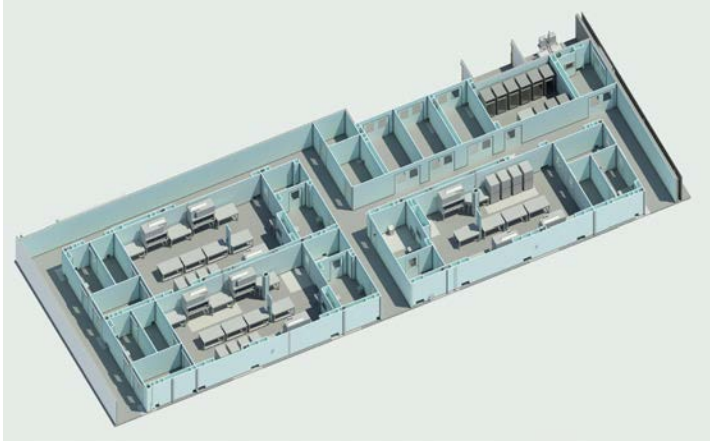
PROCESS SUITE LAYOUT OPTIONS



Multi-Patient Ballroom

*Suitable for multi-product/patient applications when employing **closed** processes.*

- Ability to implement lower cleanroom classification grades as processing background environments
- Higher patient density due to lack of walls and airlocks leading to better utilization of available facility space
- Improved suite layout for concurrent multi-patient processing and staging of in-process components
- Greatest flexibility for future repurposing of the space



Single-Patient Dedicated Suite

*Suitable for **opened or closed** processes with appropriate design features..*

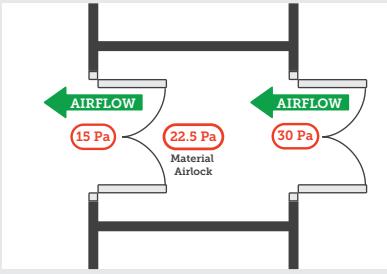
- Background environment should be ISO 7/Grade B if open processing is required, otherwise ISO 8/ Grade C is typical
- Fully dedicated HVAC system and pressurization schemes mitigate risk of cross-contamination with adjacent spaces
- Limited flexibility for reconfiguration of space due to nature of smaller sized suites
- Benefits multi-product facilities, including CDMOs, by allowing for simultaneous processing of multiple products

Design Group has experience integrating client requirements to harmonize FDA and EU regulations to establish a compliant and robust manufacturing processing facility.

Design Considerations

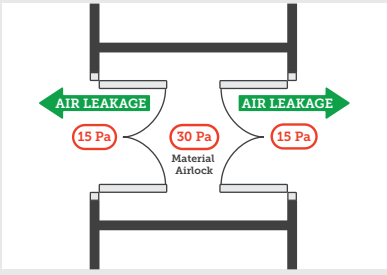
CONTAINMENT METHODS

These containment methods utilize pressurization across airlocks to ensure product quality and patient safety. Dedicated personnel and material airlocks should be employed to transition between cleanroom spaces of different environmental classification grades.



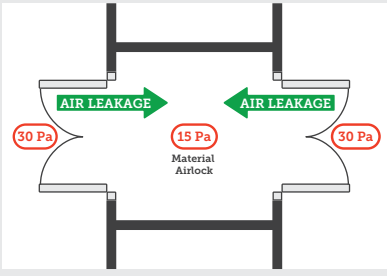
CASCADE AIRLOCK

Employed to minimize risk of product contamination is paramount and operators outside of cleanroom do not need protection from the product. Air flows from the higher ISO classification (higher pressure) to the lower ISO classfication (lower pressure). This prevents particulate matter from the lower ISO classification entering the higher ISO classification.



BUBBLE AIRLOCK

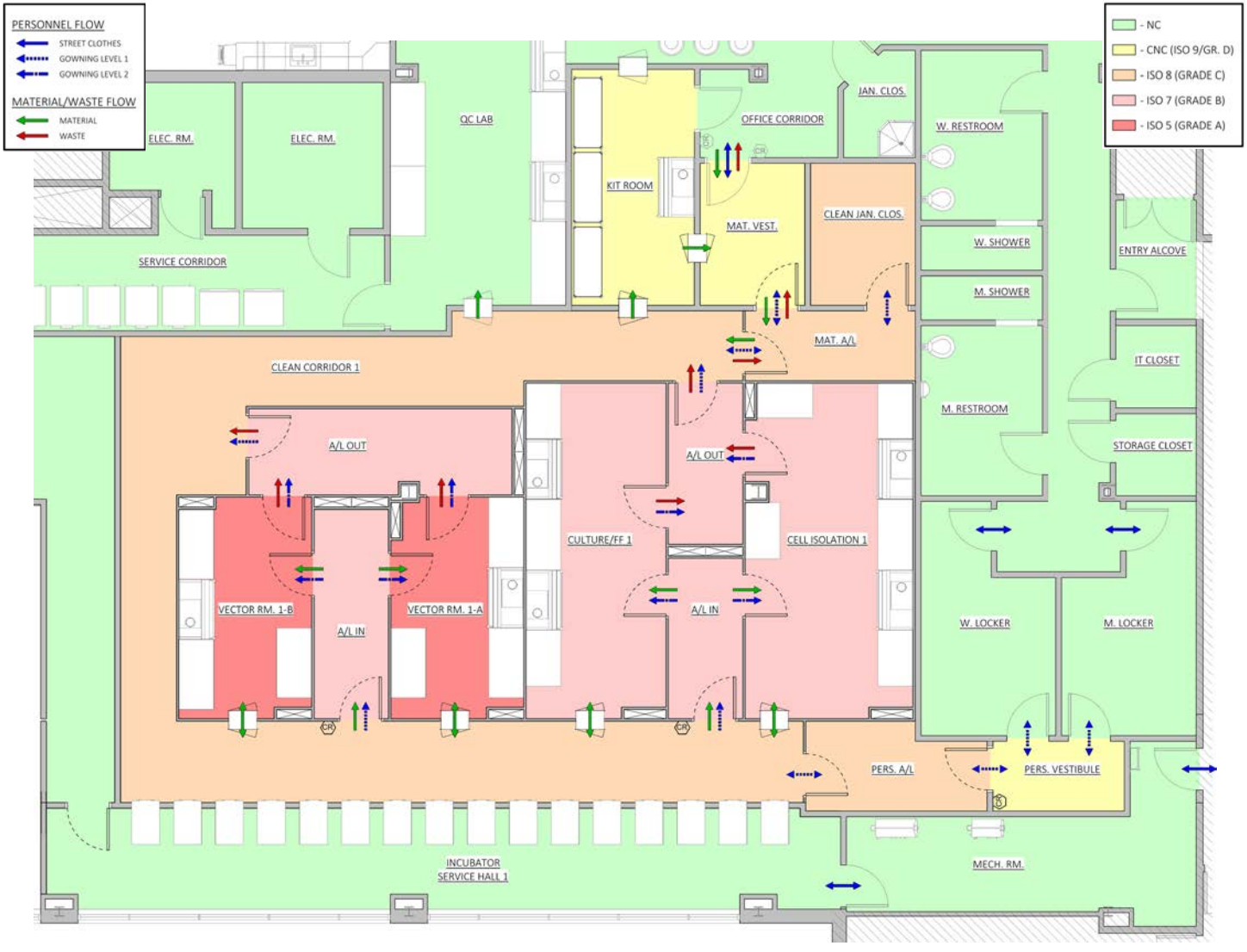
Employed when minimizing risk of product contamination and operator protection are both important (i.e., biological processes utilizing viral vector). Air flows outward bidirectionally from the airlock (higher pressure) to the adjacent spaces (lower pressure). Environmental conditions in the bubble airlock shall be that of the highest ISO classification into which air flows. Suitable for use adjacent to manufacturing rooms utilizing Biosafety Level (BSL) 1 and 2 biological hazards.



SINK AIRLOCK

Employed when producing hazardous agents that must be contained in one location. Commonly used in conjunction with an adjacent bubble airlock for infectious agents and potent compound manufacturing.

General Arrangement Sample



CLEANROOM ENVIRONMENTAL CLASSIFICATION COMPARISON

ISO Classification *(in operation 0.5 µm particles/m³ allowed)*[1]	EC Grade *(in operation 0.5 µm particles/m³ allowed) [at rest 0.5 µm particles/ m³ allowed]*[2]	Typical Air Changes per Hour (ACH)	Application of Room Classification/Notes
ISO 5 (3,520)	Grade A (3,520) [3,520]	Design criteria based on a laminar flow velocity of 0.45 m/s +/-20%	Zone for high-risk operations: • Filling zone, stopper bowls, open ampoules/vials • Open processing / manipulations of non-terminally sterilized C&GT product.
ISO 7 (352,000)	Grade B (352,000) [3,520]	60 ACH in processing areas 40 ACH in support rooms, airlocks, corridors	• Background environment for an ISO 5 / Grade A zone. • Process support rooms where no airlock exists between processing room and support room.
ISO 8 (3,520,000)	Grade C (3,520,000) [352,000]	30 ACH	Zone for less critical operations: • Background environment for fully closed processes. • Media/buffer prep that will be sterile filtered prior to use.
ISO 9/Monitored CNC (No Requirement)	Grade D (No Requirement) [3,520,000]	25 ACH in support rooms, airlocks, gowning 15 ACH in storage rooms, corridors	• Process support rooms, storage rooms, corridors, gowning & airlocks from non-classified spaces entering a classified space.

1 International Organization for Standardization (ISO) Classifications from ISO 14644-1:2015
2 European Commission (EC) Grades from EudraLex Volume 4 Annex 1 (2008)

FACILITY DESIGN BEST PRACTICES

Minimizing the possibility of cross contamination is paramount when designing a multi-product/patient facility. Unidirectional personnel and material flow in and out of critical processing areas is one key design practice to ensure multiple products remain segregated. In addition, using separate air supplies to different classification areas in combination with differential pressures between these areas creates another level of segregation to maintain the highest level of control.

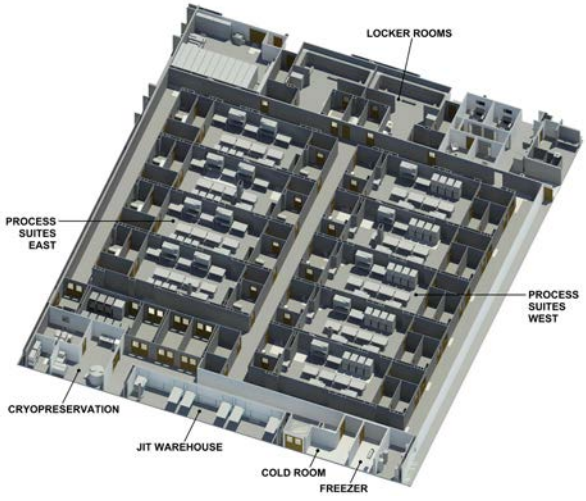
Cell & Gene Therapy Manufacturing Facility

Cognate BioServices - A Charles River Company is the leading contract development and manufacturing organization (CDMO) specializing in large late-phase clinical trials for cell and cell-mediated gene therapies. Cognate's validated cGMP multi-suite, segregated cleanroom operations provide a compliant environment with trained staff suitable for concurrent manufacturing of multiple clients and gene therapy products.

Design Group partnered with Cognate to provide EPCMV services to complete the Engineering, Procurement, and Construction Management to expand manufacturing capacity aligned with FDA & EU regulatory guidance and business needs.

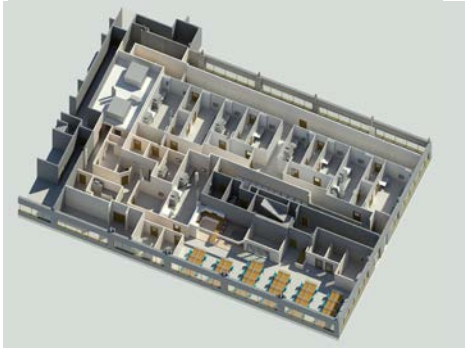
Project Scope

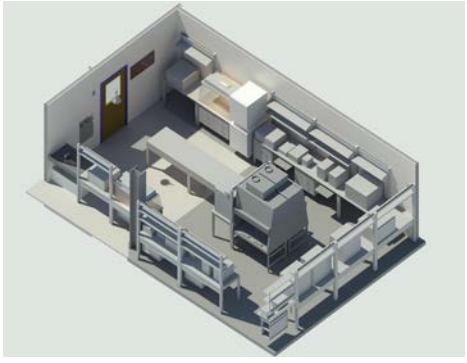
The facility expansion adjacent to existing cGMP operations required site planning and construction segregation to mitigate all risks to ongoing clinical manufacturing while sequencing construction to complete renovation of existing space. The design incorporated installation of modular cleanrooms and integration of support functions required to provide complete processing of patient product.



CAR-T & Gene Therapy Manufacturing Facility

Mustang Bio is a clinical-stage biopharmaceutical company headquartered in Worcester, MA, operating as a partner company of Fortress Biotech. Mustang Bio's state-of-the-art facility with cleanroom operations produces early-stage clinical products using CAR-T immunotherapies and gene therapies with the capability for commercialization. The products are targeted for multiple diseases, including hematologic cancers, solid tumors, and X-linked severe combined immunodeficiency (X-SCID).



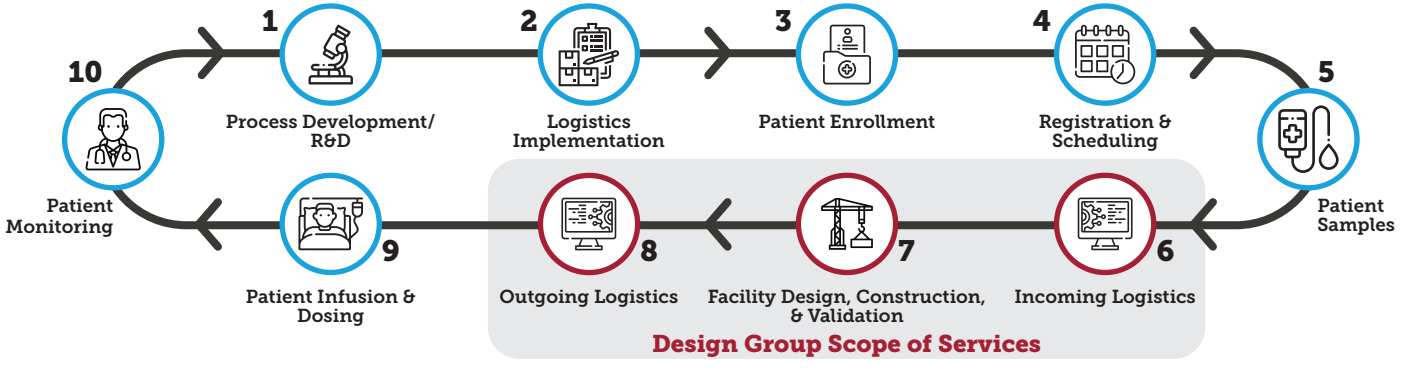


Design Group partnered with Mustang Bio to complete the engineering design to provide sealed drawings used for bidding and permitting to expand capacity for commercial manufacturing and increased laboratory capacity to align with FDA & EU regulatory guidance and business needs.

Project Scope

The multi-phase Engineering Design allowed incremental facility expansion to align with business priorities to expand office, laboratory, and commercial manufacturing while allowing ongoing clinical manufacturing.

CELL & GENE THERAPY VALUE STREAM



PCS/EMS System Design & Integration

Autolus is a biopharmaceutical company developing next generation programmed T-cell therapies for the treatment of cancer. Autolus focuses on developing T-cell programming and manufacturing technology to take products into clinical trials and provide clinical, process development, manufacturing, regulatory, health economics and market access expertise.

Design Group partnered with Autolus to evaluate and deliver manufacturing automation systems, developed system architecture, control platforms, and platform integration strategies for the for new cell processing suites in preparation for commercial manufacturing readiness.

Project Scope

The system integration solution for Process Control and Environmental Monitoring Systems (PCS/EMS) utilized cloud-based computing assets and on-premise data concentrator PLCs to monitor, analyze, and archive critical process parameters. The final design of the PCS/EMS included device integration across multiple suppliers, platforms, data collection, visualization and reporting in a validated environment.

Project Definition	Electrical & Control System Engineering					System Turnover
PFD	Electrical Definition	System Engineering & Design Specifications	Vendor/ Contractor Assessments & Bid Package Development	Procurement Services	Construction Management	Installation Check Out/System Prep
P&ID						
Equipment Layout	Software Development Lifecycle					Commissioning & Qualification
Sequence of Operation	Software Functional Design	Software Detailed Design	Software Development & In-Process Verification	Software Factory Acceptance Test		
User Requirements Document						Project Close-out

Industry & Regulatory References

The US FDA Center for Biologics Evaluation and Research (CBER) and the European Medicines Agency (EMA) have responsibility for regulating Advanced Therapy Medicinal Products (ATMPs), informed by expert committees. The ATMP regulatory framework to protect patient safety continues to evolve, harmonized with the expanding technological and scientific advances.

The concepts in this document and industry standards for design are based on the publication dates of the following guidance:

- 21 CFR 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals
- EudraLex Volume 4 Good Manufacturing Practice, Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products
- EudraLex Volume 4, Annex 1: Manufacture of Sterile Medicinal Products (corrected)
- ISO 14644-1: 2015 Cleanrooms and associated controlled environments Part 1: Classification of air cleanliness by particle concentration
- ISPE Baseline Guide, Volume 3, Sterile Product Manufacturing Facilities, Third Edition
- FDA-2003-D-0145: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice

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