Skill Standards and Curriculum for Cell and Gene Therapy Technicians

 This project was developed with an award from the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and financial assistance from the U.S. Department of Commerce, National Institute of Standards and Technology (70NANB17H002).

NIIMBL The National Institute for Innovation in Manufacturing Biopharmaceuticals

Forsyth Tech Community College · MiraCosta College · Montgomery County Community College · Quincy College · Shoreline Community College · Solano Community College

About this Report

This report and the work documented within, was developed with an award from the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and financial assistance from the U.S. Department of Commerce, National Institute of Standards and Technology (70NANB17H002). NIIMBL is one of 16 Manufacturing USA Institutes that establishes networks of public–private partnerships that work with academic and private sector manufacturing organizations on research and development and manufacturing skills training. Each institute focuses on a particular advanced manufacturing specialty such as biomanufacturing.

The Workforce Expansion in Biomanufacturing Emerging Technologies (WE–BET) initiative (NIIMBL Project 2.2–152) addressed the challenge of expanding the workforce that will produce cell–based and gene therapies. It utilized an existing decades–long collaboration network of community and technical colleges to develop Skill Standards and curriculum that will enable educators at hundreds of colleges across the United States to teach the knowledge and skills that will prepare a graduate to enter these emerging fields.

Six regions were selected for the project based on evidence and the study team's knowledge of where cell and gene therapy companies are located and thriving. The community college partners in these regions were chosen for their geographic location and expertise. Each college is centrally located within a region that has a significant Biotechnology industry cluster. The involvement of colleges from different regions will enable the production of a national, harmonized curriculum. Each region, community college and the college lead is listed below:

Region	Community College	Lead(s)
San Francisco Bay region	Solano Community College (Vacaville, CA)	Jim DeKloe
San Diego region	MiraCosta College (Oceanside, CA)	Barbara Juncosa, Dominique Ingato
Seattle region	Shoreline Community College (Seattle, WA)	Louise Petruzzella
Philadelphia region	Montgomery County Community College (Blue Bell, PA)	Margaret Bryans, Hetal Doshi
Boston region	Quincy College (Quincy, MA)	Isso Bayala
North Carolina	Forsyth Technical Community College (Winston–Salem, NC)	Russ Read

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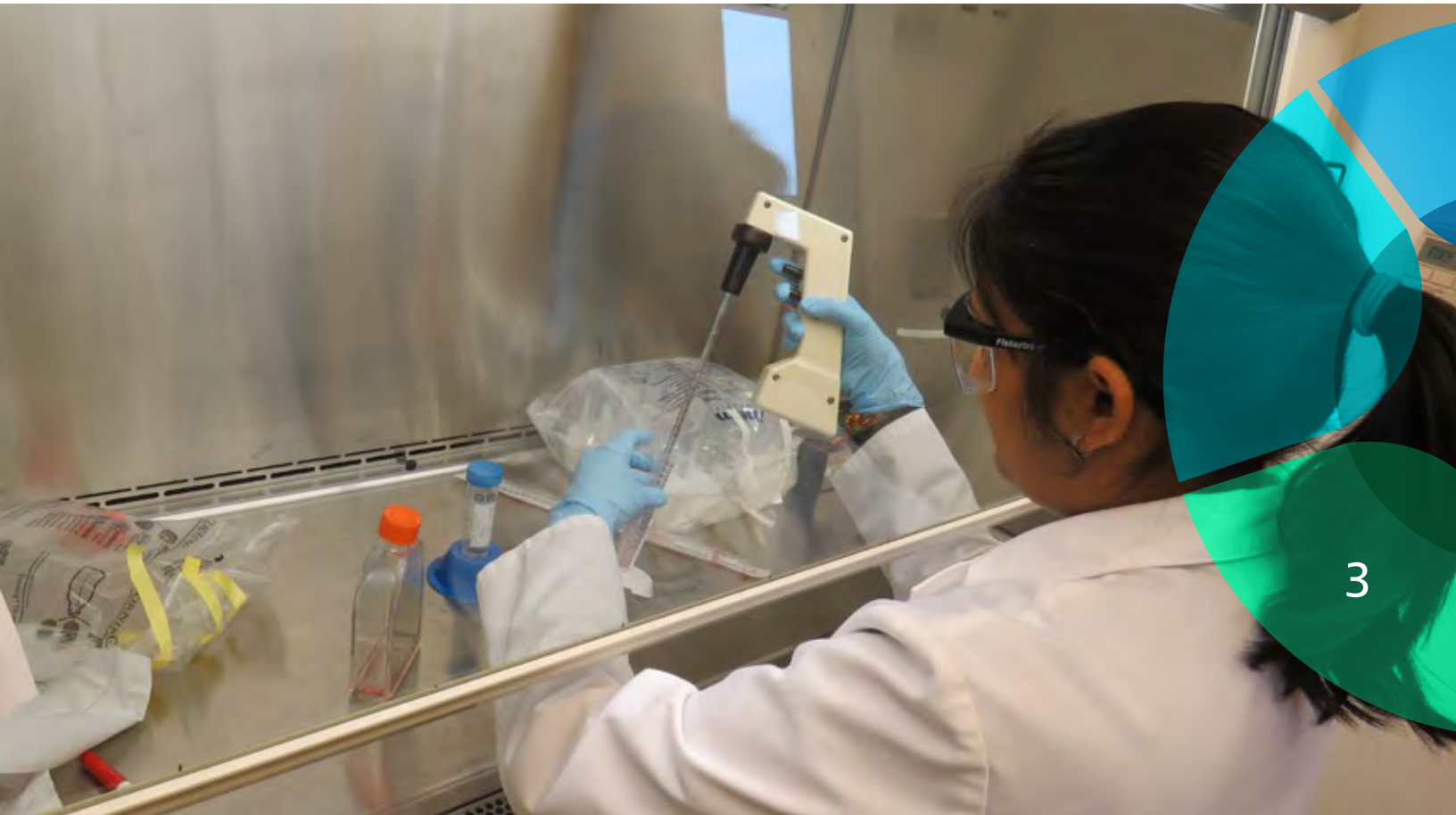

Process for Developing Skill Standards for Cell and Gene Therapy Technicians

Industry Subject Matter Experts (SMEs) generated the Skill Standards for Cell and Gene Therapy Technicians. This study gathered experts in each of the six targeted geographic regions considered hubs of cell and gene therapy: San Francisco Bay, North Carolina, Philadelphia, San Diego, Boston, and Seattle.

In each hub, SMEs reviewed Skill Standards that had been previously developed by the Northeast Biomanufacturing Center and Collaborative for technicians in "traditional biomanufacturing" (the production of vaccines, monoclonal antibodies and other pharmaceutical proteins) with a focus on upstream and downstream processing and quality control. SMEs from each geographic hub reviewed the Standards together in a facilitated meeting. A total of twenty-seven companies and three academic institutions were represented. Most of the SMEs had worked in pharmaceutical protein production before branching out into cell or gene therapy and brought that experience into the discussion.

They applied their wealth of experience to answer the question, **"how do the knowledge and skills required for an entry-level technician to excel in cell and gene therapy differ from those required in 'traditional biomanufacturing'?"** SMEs also rated the Key Activities performed by cell and gene therapy technicians as either critical, important or desirable.

The study team compiled the SME responses to produce these Skill Standards.

What are Skills Standards?

Skill standards are performance specifications that identify the knowledge, skills and abilities an individual needs to succeed in the workplace. They provide a framework for educators to develop curriculum, courses and credentials as well as measureable learning outcomes. They indicate to students the skills needed in the workplace and just as importantly, give them the terminology to describe and discuss their skill set. They offer common language with which educators and industry can discuss training requirements to ensure that industry is provided withthe technical workforce it needs to remain competitive.

Format and Terminology

The study team created the following format and terminology in order to make the Skill Standards more useful to all stakeholders:

Critical Work Functions are the broadest areas of responsibility for entry-level cell and gene therapy technicians. Critical Work Functions are general enough that the vast majority of entry-level technicians have job descriptions that encompass them.

A Key Activity is an essential task performed by a technician on a regular basis. Key Activities are specific enough that students or entry-level workers can be assessed to determine their level of mastery.

How this activity differs from traditional biomanufacturing provides information from industry subject matter experts about how cell and gene therapy technicians would perform the Key Activity compared to a technician in a traditional biomanufacturing setting.

Skill Standards for Cell and Gene Therapy Technicians

Skill Standards for Both Cell and Gene Therapy Technicians

CRITICAL WORK FUNCTION:
Perform Basic Manufacturing Operations

Key Activity: Inspects or samples materials at all stages of process to determine quality or condition.

How this activity differs from traditional biomanufacturing:

- Since the product is cells or viruses instead of a protein drug the specific types of samples and analysis differs.

Key Activity: Operates, monitors, and maintains equipment, tools, and workstation (e.g., HMI, process control systems).

How this activity differs from traditional biomanufacturing:

- There is considerable overlap in equipment used but CGT has specific equipment unique to their production e.g. cell processors, cell sorters.

Key Activity: Participates in troubleshooting, trend analysis, and root cause analysis of operations.

How this activity differs from traditional biomanufacturing:

- Due to the time sensitivity these activities are performed with a higher sense of urgency.

CRITICAL WORK FUNCTION:
Perform Upstream Manufacturing Operations

Key Activity: Performs vial thaw from a cell or virus bank.

How this activity differs from traditional biomanufacturing:

- The source material is limited in cell therapy with patient apheresis generating the starting material. In gene therapy, a virus bank is generated in addition to a cell bank.

Key Activity: Performs cell culture expansion (scale-up).

How this activity differs from traditional biomanufacturing:

- Viral vector expansion process is similar but smaller scale than commercial biopharmaceutical production.
- Either adherent or suspension culture are used to produce the viral product.
- Cell culture exclusively uses single use technology.
- Requires open aseptic processing expertise more often than in the production of traditional biologics.
- Cell expansion process is different for cell therapy – smaller scale and, different equipment used.

Key Activity: Monitors cell concentration by cell counting methods.

How this activity differs from traditional biomanufacturing:

- Often the cell counting methods are different for cell therapy.
- Cell counts are normally done by gating on cell size using multisizer or by nuclear staining since patient sample has diverse cell types which differs from uniformly sized CHO cells.
- For cell therapy the sample must be small since the amount of material is very limited and precious.
- Different equipment/procedures are used – flow cytometry is common.

Key Activity: Inoculates seed and/or expansion reactors.

How this activity differs from traditional biomanufacturing:

- Smaller scale bioreactors with no stainless steel. Wave type bioreactors and single use technologies are used exclusively.
- Process differs for cell therapy, and typically has a smaller scale, shorter process, different equipment.
- In cell therapy there are unique treatments to the cells including T cell activation.
- Viral vector manufacturing can utilize adherent cells in cell factories.

Key Activity: Monitors and maintains controlled conditions for growth of cells in culture vessels.

How this activity differs from traditional biomanufacturing:

- The process is a little different for cell therapy, because of the smaller scale, different equipment and closed bioreactors.
- In cell therapy because of scale out rather than scale up multiple bioreactors must be monitored and controlled.

Key Activity: Performs aseptic additions of media, solutions, and/or gases to reactors.

How this activity differs from traditional biomanufacturing:

- The process is a little different for cell therapy, because of the smaller scale, different equipment and smaller additions.
- Single use bioreactors require skills in aseptic connectors and aseptic tube welding.

Key Activity: Performs aseptic sampling.

How this activity differs from traditional biomanufacturing:

- The process is a little different for cell therapy, because of the smaller scale, different equipment and smaller additions.
- Single use bioreactors require skills in aseptic connectors and aseptic tube welding.
- For cell therapy smaller volumes are used for sampling.

Key Activity: Labels samples.

How this activity differs from traditional biomanufacturing:

- Similar to traditional biomanufacturing.
- Traceability and data integrity are heightened in cell therapy where the patient's sample is precious and may be irreplaceable based on patient's health status.

Key Activity: Performs transfection, infection and transduction.

How this activity differs from traditional biomanufacturing:

- This is not part of the biomanufacturing process in traditional biomanufacturing.
- **Gene Therapy:** Triple transfection, plasmid additions, viral production.
- **Cell Therapy:** Recombinant virus transduction, time sensitivity.

CRITICAL WORK FUNCTION:
Perform Downstream Manufacturing Operations

Key Activity: Separate viruses or cells from media using centrifugation or filtration.

How this activity differs from traditional biomanufacturing:

- Separation of cell types in cell therapy.
- Filtration rather than centrifugation.
- Smaller scale and single use filtration units used.
- For cell therapy, the downstream process differs considerably. Cells are the end product, formulation and cryopreservation, are critical.
- Single use connector technology and tube welding process are important.

Key Activity: Performs final fill of product.

How this activity differs from traditional biomanufacturing:

- Smaller scale.
- For cell therapy speed of execution is required, bag technology is used.

Key Activity: Maintains cold chain.

How this activity differs from traditional biomanufacturing:

- This activity is used at fewer stages of the process in traditional biomanufacturing.
- Cold chain is critical in cell therapy, it is central to the process. The process starts and ends with cold chain essential to the starting material and the product.

CRITICAL WORK FUNCTION:
Perform Laboratory Work

Key Activity: Prepares reagents.

How this activity differs from traditional biomanufacturing:

- The process is different for cell therapy, it is smaller scale, different equipment used, strictly single use.

Key Activity: Performs sample receipt (stability, in-process, water, raw materials, final product, environment, validation) per batch records or plans.

How this activity differs from traditional biomanufacturing:

- The process is different for cell therapy because of the smaller scale.
- Modified plans due to individual batches (1 patient/batch) and therefore chain of identity is important.
- Increased criticality of the samples received due to limited therapeutic material. Every milliliter of sample that is used for quality control is diverted from the patient.

Key Activity: Qualifies and maintains reference standards.

How this activity differs from traditional biomanufacturing:

- Outsourcing very common, contracted testing facility retains standards.

Key Activity: Maintains reference cultures.

How this activity differs from traditional biomanufacturing:

- Outsourcing very common, contracted testing facility retains cultures.

Key Activity: Prepares samples for analysis.

How this activity differs from traditional biomanufacturing:

- Sample type differs (e.g. virus, cells).
- For cell therapy much smaller volumes are used for sampling.
- Increased criticality of proper sample preparation.

Key Activity: Performs upstream testing.

How this activity differs from traditional biomanufacturing:

- Types of tests differs e.g. fluorescent nuclear staining techniques common for cell counting.
- For cell therapy flow cytometry is an important technique.

Key Activity: Performs downstream testing.

How this activity differs from traditional biomanufacturing:

- Testing differs in cell therapy since downstream processing is not traditional purification but a combination product using various instruments to load and package drug substance aseptically.
- For gene therapy droplet digital PCR, capillary electrophoresis, HPLC and cell based assays commonly used.

Key Activity: Evaluates data according to specifications.

How this activity differs from traditional biomanufacturing:

- Different types of data generated and evaluated.

CRITICAL WORK FUNCTION:
Perform Microbiological Testing and Culturing

Key Activity: Prepares working cell or virus bank.

How this activity differs from traditional biomanufacturing:

- The testing of cell banks and virus banks is often outsourced.

Key Activity: Tests sterilization cycles with biological indicators and perform sterilization procedures.

How this activity differs from traditional biomanufacturing:

- Because of the dominance of single use equipment, autoclaves are rarely used.

Key Activity: Performs microbial identification.

How this activity differs from traditional biomanufacturing:

- This activity is often outsourced.

Key Activity: Tests for virus.

How this activity differs from traditional biomanufacturing:

- This activity is often outsourced.

Key Activity: Tests for mycoplasma.

How this activity differs from traditional biomanufacturing:

- This activity is often outsourced.

Key Activity: Tests for endotoxin/pyrogen (e.g., water, in-process, final product).

How this activity differs from traditional biomanufacturing:

- Limulus Amebocyte Lysate rapid test or contracted out.

Key Activity: Tests for bioburden (e.g., water, in-process, final product).

How this activity differs from traditional biomanufacturing:

- This activity is often outsourced.
- Rapid sterility test.

Key Activity: Tests for quality of media/reagents using growth promotion tests.

How this activity differs from traditional biomanufacturing:

- This activity is often outsourced.
- QC qualification of aseptic processing.
- Rapid sterility tests are important.
- Transfection reagents must be tested.

Key Activity: Conducts sterility testing on in-process materials and/or finished products.

How this activity differs from traditional biomanufacturing:

- This activity is often outsourced.
- Rapid sterility testing for cell therapy due to time constraints e.g BacT.
- In cell therapy the final product cannot undergo a final sterilization step so sterile conditions must be maintained throughout the process.

Key Activity: Performs Environmental Monitoring.

How this activity differs from traditional biomanufacturing:

- Very similar to traditional biomanufacturing.

CRITICAL WORK FUNCTION:
Perform Chemical and Biochemical Testing

Key Activity: Performs biochemical or bioassay testing for identity, potency, purity, consistency and/or stability.

How this activity differs from traditional biomanufacturing:

- Analytical techniques are different.
- For gene therapy, product specific bioassays for potency are often contracted out.
- For cell therapy, imaging based co-culture assays used.

Key Activity: Performs chemical and biochemical testing for raw material, water and other environmental and validation samples.

How this activity differs from traditional biomanufacturing:

- In many cases, raw material testing contracted out.
- In early phases many raw materials are accepted based on Certificate of Analysis.

CRITICAL WORK FUNCTION: Managing Information

Key Activity: Utilizes computer systems to manage data.

How this activity differs from traditional biomanufacturing:

- QC/Manufacturing Sciences and Technology would usually manage Manufacturing Execution System entry/data.

Key Activity: Supports data trending activities.

How this activity differs from traditional biomanufacturing:

- QC/Manufacturing Sciences and Technology responsibility.
- Not typically a requirement at the entry level technician position.

Key Activity: Generates technical reports.

How this activity differs from traditional biomanufacturing:

- QC/Manufacturing Sciences and Technology responsibility.
- Not typically a requirement at the entry level technician position.

CRITICAL WORK FUNCTION: Work in Compliance with cGMPs and Other Regulatory Requirements

Key Activity: Performs environmental monitoring activities.

How this activity differs from traditional biomanufacturing:

- May have more rigorous environmental obligations for viral and cell based products.
- Samples are taken during production, by Quality Control technicians.

Key Activity: Records data and documents activities (e.g., paper hard copy and/or electronically).

How this activity differs from traditional biomanufacturing:

- Controlled documents are very similar to traditional biologics manufacturing.

Key Activity: Orders raw materials, parts, components and/or equipment.

How this activity differs from traditional biomanufacturing:

- There is an increased responsibility for daily kitting, this is critical due to single use technology constraints.

Key Activity: Receives and stores raw materials, parts, components and/or equipment.

How this activity differs from traditional biomanufacturing:

- In cell therapy, receiving raw material is a critical part of the process.
- Maintaining the chain of identity is critically important.
- Cold chain management is critically important for cell therapy.
- If a facility is producing products for clinical trials in addition to marketed products the procedure for storage and release of materials may be different.

Key Activity: Handles raw materials, parts, components and/or equipment.

How this activity differs from traditional biomanufacturing:

- Cells sometimes must be processed immediately.
- In cell therapy, the patient's cells are the raw material. It is critical to the success of the process that these cells be handled properly.
- The cells that serve as raw material often vary in quality.
- The cells that serve as raw material are very limited in quantity.

Key Activity: Participates in cGMP and specific training.

How this activity differs from traditional biomanufacturing:

- GMP training is critical in both traditional and emerging biomanufacturing.

Key Activity: Documents and/or maintains individual training.

How this activity differs from traditional biomanufacturing:

- Maintenance of training records is critical in both traditional and emerging biomanufacturing.

Key Activity: Works with equipment and processes in a validated state.

How this activity differs from traditional biomanufacturing:

- Many cell therapy companies are start-ups that are not at the point of process validation, but still require qualified equipment and follow SOPS.
- This can vary depending on the stage of the program. Equipment may be "less validated" for the newer technologies.

Key Activity: Follows appropriate flow of personnel, equipment, and materials.

How this activity differs from traditional biomanufacturing:

- Technicians should have a basic knowledge of facility design including flow of personnel equipment and materials.
- Flow is adjusted to accommodate to the presence of a viral vector in the unit operation. There is a one-way flow for viral vector material.

Key Activity: Updates, labels, and applies status to equipment and materials.

How this activity differs from traditional biomanufacturing:

- Since single use technology dominates, material and equipment are already labelled. Proper labelling of product and samples is essential.
- Chain of identity is critical in cell therapy.

Key Activity: Identifies and reports exception/deviation events.

How this activity differs from traditional biomanufacturing:

- The identification and proper documentation of deviations are critical in both traditional and emerging biomanufacturing.

Key Activity: Reviews and/or verifies data.

How this activity differs from traditional biomanufacturing:

- Reviewing and verifying data is important in both traditional and emerging biomanufacturing.

Key Activity: Participates in change control activities.

How this activity differs from traditional biomanufacturing:

- Change control activities are more common in younger companies than in established biomanufacturing plants and therefore technicians are likely to be more involved in change control.
- In cell therapy, the variability of the patient cell raw material requires more frequent changes to the process.

Key Activity: Archives documentation/data.

How this activity differs from traditional biomanufacturing:

- The archiving of data is essential in both traditional and emerging biomanufacturing.

Key Activity: Maintains data integrity.

How this activity differs from traditional biomanufacturing:

- Data integrity continue to be a focus for improvement in both traditional and emerging biomanufacturing.

Skill Standards for Gene Therapy Technicians (Only)

CRITICAL WORK FUNCTION:
Perform Downstream Manufacturing Operations

Key Activity: Performs cell disruption techniques (e.g., mechanical or chemical).

How this activity differs from traditional biomanufacturing:

- There is a larger focus on chemical lysis than what may be traditional for mammalian culture activities.
- Physical cell disruption (homogenizers) is used less in gene therapy production than in traditional biomanufacturing.

Key Activity: Performs chemical/enzymatic modifications to product.

How this activity differs from traditional biomanufacturing:

- DNase treatment is used for DNA removal.

Key Activity: Prepares equipment for normal flow and tangential flow filtration (e.g. including microfiltration, ultrafiltration, or diafiltration).

How this activity differs from traditional biomanufacturing:

- Preparation is different because single use filtration units are used.
- Smaller scale and single use disposables.
- Usually a hollow fiber tangential flow filtration system is used.

Note: *Knowledge of this is useful for Cell Therapy, but not a Key Activity.*

Key Activity: Performs normal flow and tangential flow filtration (e.g. including microfiltration, ultrafiltration, or diafiltration).

How this activity differs from traditional biomanufacturing:

- Smaller scale and single use disposables.
- Usually a hollow fiber TFF system is used.

Note: *Knowledge of this is useful for Cell Therapy, but not a Key Activity.*

Key Activity: Prepares chromatography columns (e.g., assembly, sanitization, resin packing, validation).

How this activity differs from traditional biomanufacturing:

- Smaller columns and skid.
- Prepacked columns used, therefore resin packing not performed.
- Multiple resins – especially affinity and ion exchange chromatography resins.
- Single use tubing assembly used.

Key Activity: Performs chromatography steps (e.g., equilibrate, load, wash, elute, clean, store).

How this activity differs from traditional biomanufacturing:

- There are smaller columns and skids, as well as smaller buffer volumes.

Key Activity: Performs viral clearance (e.g. removal/inactivation) steps.

How this activity differs from traditional biomanufacturing:

- Many gene therapy products are viruses themselves but there will be a validated step to remove contaminating viruses.
- Viral clearance step(s) differs from traditional biomanufacturing.

Skill Standards for Cell Therapy Technicians (Only)

CRITICAL WORK FUNCTION: Perform Basic Manufacturing Operation

Key Activity: Performs cell culture expansion.

How this activity differs from traditional biomanufacturing:

- Scale of manufacturing is much smaller for autologous cell manufacturing. The process involves "scale-out rather than scale-up".

CRITICAL WORK FUNCTION: Perform Downstream Manufacturing Operations

Key Activity: Maintains chain of identity and chain of custody.

How this activity differs from traditional biomanufacturing:

- This critical activity is not performed in traditional biomanufacturing.

CRITICAL WORK FUNCTION: Work in Compliance with cGMPs and Other Regulatory Requirements

Key Activity: Complies with HIPAA requirements.

How this activity differs from traditional biomanufacturing:

- Must comply with the Health Insurance Portability and Accountability Act (HIPAA) as patient data may be visible to technicians. This is not a requirement for traditional biomanufacturing.

Curriculum for Training Cell and Gene Therapy Technicians

Curriculum for Training Cell and Gene Therapy Technicians

Industry Subject Matter Experts were asked a series of open ended questions about what should be included when designing a course on Cell Therapy or Gene Therapy, and the non-technical skills that should be emphasized.

The answers provided valuable information which is the basis for the curriculum content in this section. **For each course, the following information is provided:**

- Foundational Knowledge
- Laboratory Skills and Technology
- Manufacturing Process
- Non-technical workplace skills

Topics to cover in a Cell Therapy course designed for entry level students or employees:

Foundational Knowledge

- Fundamentals of Immunology, Cell biology, and Virology
- Basic concepts of biotechnology and molecular biology
- Landscape of Cell Therapy:
  - Types of cell products approved and in development
  - Allogeneic cell therapy and autologous cell therapy
  - Case studies
  - The key differences and challenges between standard biologics manufacturing and cell therapy manufacturing (scale, criticality, variability of starting material)
- Autologous Cell Therapy:
  - Direct impact on patient, turn-around time and criticality of doing it right the first time
  - Strong emphasis on aseptic processing and quality
  - Scale-out and not scale-up
  - Variability of patient starting material
  - Shipping control and logistics for handling living cells to and from patient
  - Methods and equipment used for apheresis like cell sorter, Ficoll based gradient centrifugation etc.
  - Genetic modification
- Allogeneic Cell Therapy:
  - Cell types
  - Scale-up process
  - Genetic modification
  - Challenges
- Introduction to regulatory environment and quality control/assurance – cGMP/GXP, good documentation practice, specifications testing, control of materials.
- Data analysis, process trending

Laboratory Skills and Technology

- Aseptic Technique and Cell Culture Skills:
  - **Basics in cell handling:** aseptic technique, media preparation, cell counting, doubling time, growing adherent vs suspension culture, passage number, fundamentals of what each step/reagent is actually doing biochemically, identify the densities of the cells in the culture vessel
  - An understanding of cell biology in detail to consider cell health throughout a production process
  - Good practices for gowning to work in a biological safety cabinet. Biological safety cabinet (BSC) training e.g. practices to avoid air disruption
  - Segregation of material, cross contamination, staging of materials in BSC, sterility
  - Open vs closed processing, associated risks, and contamination control
- QC assays including cell counting, cell viability, vector copy number, flow cytometry, replication competent lentivirus etc.
- Flow cytometry/FACS analysis
- Cell phenotyping by surface markers
- Traditional qPCR, droplet digital PCR
- Custom Assay development and matrix approach

Manufacturing Process

- High level process overview with major unit of operations including main equipment and methods that can be used at each step
- Patient material receipt, inspection, and release for processing
- Variability in the starting material (i.e. patient cells) which can introduce upstream complexity and variability into the production process
- Chain of custody/chain of identity
- Gene Delivery (Electroporation, CRISPR, ZFNs, lentivirus, AAV etc.)
- Expansion
- Harvest/filtration
- Cryopreservation
- Packaging, freezing, shipping, and delivery of the modified cell into patient
- Single use technology: bioreactors, sterile tube welder, sterile connectors
- Operation of equipment that can be used during processing such as pumps, centrifuges, cell washers, Plasmatherm, control rate freezer, automated cell processing (e.g., CliniMACS Prodigy)
- Open vs closed processing, associated risks, and contamination control
- Microbiological Control, endotoxin test, Rapid Sterility Tests, mycoplasma testing, particle counter and environmental monitoring
- All aspects of Quality Assurance, Quality Control, Environmental Health & Safety, deviations, CAPA (Corrective Action, Preventative Action)
- Focus on importance and life-saving/ changing nature of products
- Single source suppliers for materials and equipment
- Labor and material cost are extensive.
- Electronic Batch records and digital lab notebook

Topics to cover in a Gene Therapy course designed for entry level students or employees:

Foundational Knowledge

- Cell biology, Genetics, Immunology, Microbiology and Virology
- Basic concepts of biotechnology and molecular biology
  - Gene expression, cell transfection/transduction, quantitative PCR, gene editing, DNA/Gene sequencing, plasmid construction, viral vectors
- Fundamentals of virology and why different viruses (and different serotypes) are used for different types of diseases (limitations and strengths of different viruses)
- Landscape of Gene Therapy:
  - Gene therapy versus protein therapy
  - Types of gene therapy
  - Molecular level understanding of basic process and mechanism of action of gene therapy
  - Types of viral vectors their components and design, different gene delivery methods (lipid/amino acids based nanoparticles, AAV, lentiviruses etc.)
  - Vector production
  - Case studies
- Overview of gene therapy drug development process
- Potency testing – custom assay development and matrix approach
- FDA structure and approval process
- Comparison between small molecule, biologics and cell and gene therapy processing
- Lab math, basic statistics, critical thinking, problem solving and flexibility

Laboratory Skills and Technology

- Aseptic Technique and Cell Culture Skills:
  - **Basics in cell handling:** aseptic technique, media preparation, cell counting, doubling time, growing adherent vs suspension cells in culture, passage number, fundamentals of what each step/reagent is actually doing biochemically, identify the densities of the cells in the culture vessel
  - An understanding of cell biology in detail to consider cell health throughout a production process
  - Good practices for gowning to work in a biological safety cabinet. Biological safety cabinet (BSC) training e.g. practices to avoid disruption of air laminar flow
  - Segregation of material, cross contamination, staging of materials in BSC, sterility
  - Open vs closed processing, associated risks, and contamination control
- Scale up calculations
- Cell and virus banking
- Molecular Biology
- DNA extraction
- DNA/Gene sequencing

- Plasmid construction
- Techniques for transfection/transduction of cells
- **Analytics:**
  - SDS PAGE/ silver stain
  - ELISA assays
  - HPLC/ Size Exclusion Chromatography
  - Traditional qPCR and Digital Droplet PCR
- UV VIS Spectrophotometry
- Cell based assays for specific attributes (i.e. functional assays like insulin release from pancreatic islets, contractility of cardiomyocytes, etc)
- Lab math, critical thinking, problem solving and flexibility

Manufacturing Process

- High level process overview with major unit of operations including main equipment and methods that can be used at each step
- Adherent versus suspension process
- Single use technology, bioreactors, sterile tube welder, sterile connectors, single use chromatography skids and filtration units
- cGMP good documentation, verification, ethics, Regulatory Affairs
- Infectivity and titer determination
- Chromatography, concepts of various chromatography steps– importance of gradient in elution, column volumes, types of resin, importance of correct column packing, elution profiles, residence time, dimensions of column
- Tangential Flow Filtration, Ultrafiltration/ Diafiltration (molecular weight for cassettes selection, permeate, retentate, understanding of HMI (Human Machine Interface) screen with Tangential Flow Filtration monitoring, Trans Membrane Pressure, feed pressure, crossflow flux, hollow fiber mechanism
- Environmental Health and Safety, biohazard waste disposal, safety precautions around viral vector production, AAV and lentivirus handling and safety
- Process understanding: impact to product (viral understanding), patient, process, operator, environment
- Understanding that the material volumes are low compare to the traditional biomanufacturing process
- Zonal ultracentrifugation (density gradient)
- **Analytics:** Potency assay for gene therapy, transfection efficiency, titer determination (both viral genome and viral particle) aggregation, appearance, pH, capsid purity, capsid post translational modifications, capsid structure, residual impurities (host cell protein, DNA, viruses), Size Exclusion Chromatography combined with multiangle light scattering (MALS) and refractive index (RI) for characterization and quantification of AAV
- Microbiological Control, endotoxin test, traditional and rapid sterility tests, mycoplasma detection, particle counter and environmental monitoring
- Technical protocols and reports
- Electronic Batch records and digital lab notebooks

Most important non-technical workplace skills that Cell and Gene Therapy Technicians need:

- Detail oriented and the ability to follow procedures and step documentation
- Self-motivated and ability to integrate effectively into a team, enhancing the team's overall efficiency and productivity
- Patient-centered mindset
- Strong interpersonal skills to foster teamwork and collaboration
- Strong verbal and written communication skills, cross functional communication ability
- Respectful of others
- Emotional intelligence
- Professionalism, proper email etiquette, etc.
- Positive attitude, patience
- Critical/analytical thinking
- Being vigilant and noticing when things do not seem correct
- Good documentation
- Learning agility, coachable, open to self-development
- Efficiency mindset (thinking ahead) – prepping for the next step (obtaining sample collection labels, gathering materials, etc.) during downtime or while waiting for process to end
- The importance of maintaining a clean work station (throw waste away immediately, label everything, good organization habits)
- Knowledge of cGMP regulations and FDA guidance
- Awareness of continuous improvement concepts, Lean Sig Sigma concepts (yellow belt level in which a person participates as a team project member and reviews process improvement), accountability and clear communication
- Ability to work under pressure in a fast-paced and dynamic environment
- Broad skill base to work in multiple positions if needed
- How to maintain consistency every day when performing an assay
- Challenge the status quo
- Project management and planning
- Creating and owning development plan
- Honest and conscientious

Equipment Required for Training Cell and Gene Therapy Technicians

Industry Subject Matter Experts Recommendations for Equipment Required for Training Cell and Gene Therapy Technicians

Equipment Essential for Both Cell and Gene Therapy Courses

UPSTREAM

- Cell culture equipment
- Incubators
- Biosafety Cabinets
- Freezer/refrigerators
- Single use bioreactors
- Rocker bioreactors for mammalian cell culture (these are single use)
- Single use technologies including aseptic connector and tube welders
- Suspension cell bioreactors
- Adherent cell bioreactors
- Appropriate control units for fermentors, bioreactors
- Microscope
- Bioprocess analyzer for analyte measurement (such as a Bio HT system)
- Cell counter (such as a Vi-CELL or fluorescent nuclear staining model)

DOWNSTREAM

- Centrifuge for cell recovery/clarification; disc-stack unit would be preferable
- Depth filtration system for clarification
- Tangential flow microfiltration equipment for clarification
- (Bulk) Final filling equipment (many options here)
- Conductivity meters
- pH meters
- Bench-top centrifuge
- Freezers/refrigerators
- UV/Vis spectrophotometer

PROCESS SUPPORT

- Mixers (these could be stainless steel or single use, with single use being preferable)
- Buffer storage equipment – the need for this would depend on scale of operations
- Filter integrity tester
- Autoclave
- Glasswasher

ANALYTICAL

- Gel electrophoresis system
- Plate reader
- qPCR system
- Various smaller miscellaneous items for measurements such as endotoxin, bioburden, ELISAs, protein quantification, host cell protein quantification, host cell DNA quantification, etc.

Equipment Essential for Cell Therapy Course

UPSTREAM

- The use of antibodies to identify particular cell populations – Flow Cytometer
- Cell Type Separator technology

ANALYTICAL

- Flow Cytometry – Analytical
- Fluorescence Activated Cell Sorter

Equipment Essential for Gene Therapy Course

UPSTREAM

- Insect cell cultivation for the production of some virus vectors
- Stirred tank bioreactors for mammalian cell culture

DOWNSTREAM

- Chromatography system for product purification
- Tangential flow ultrafiltration system for product concentration, formulation

Optional Equipment for Cell and Gene Therapy Courses

UPSTREAM

- Electroporators
- Fermentors for microbial fermentation

DOWNSTREAM

- Homogenizer for cell lysis (other lysis options are available)

FILL–FINISH

- Fill machine – many sizes and varieties
- Isolator
- Freeze dryer
- Differential scanning calorimeter

PROCESS SUPPORT EQUIPMENT

- Clean-in-place equipment (the need would depend on scale)

ANALYTICAL

- High performance liquid chromatography system (HPLC)

Additional Resources

Biomanufacturing Skill Standards

The skill standards for traditional biomanufacturing (protein based biologics) developed by the Northeast Biomanufacturing Center and Collaborative (NBC2) can be found here:

http://biomanufacturing.org/curriculum-resources/resources/skill-standards

Assessments and Glossary of Terminology

Assessments used to test a worker's ability to perform tasks successfully and a glossary of terminology related to Skill Standards can be found here:

https://sites.google.com/site/c3bcbiosciencesskillstandards/

WE-BET Project Outcomes

Additional outcomes of the WE-BET project included labor market research, faculty professional development and hands-on curriculum development. Results of these initiatives can be accessed on the NBC2 website at:

http://biomanufacturing.org/curriculum-resources/program-units/manufacture-of-cell-and-gene-therapies

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