Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells

A Technology Roadmap to 2025

Developed by
National Cell Manufacturing Consortium

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Georgia Research Alliance
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Prepared by NEXIT GROUP
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About this Roadmap

Cell-based therapies—especially stem cell therapies, regenerative medicine, and immunotherapies—and cell-based devices and diagnostics could have significant public health and economic benefits but will require the cost-effective, large-scale, reproducible manufacturing of high-quality cells to realize their potential. Enabling large-scale cell manufacturing calls for resource investments in advanced technologies and techniques that can increase cell production scale and speed while improving quality assurance, reducing manufacturing and product costs, enhancing manufacturing reproducibility and consistency, strengthening information technology security, and increasing treatment efficacy and safety.

The Georgia Research Alliance (GRA) and Georgia Institute of Technology (Georgia Tech) recognized the opportunity to advance innovative technologies and techniques that can overcome current cell manufacturing challenges and support long-term growth of the cell manufacturing industry. Together, GRA and Georgia Tech established the National Cell Manufacturing Consortium (NCMC) and led the development of this roadmap, with funding from the National Institute of Standards and Technology (NIST) Advanced Manufacturing Technology Consortia (AMTech) program. This roadmap identifies challenges that currently constrain cell manufacturing and provides a pathway for developing, advancing, and implementing advanced technologies over the next 10 years to enable large-scale, cost-effective, reproducible manufacturing of high-quality cells.

The development of this roadmap was informed by a variety of stakeholder inputs, built around several highly interactive roadmapping workshops. Nearly 100 cell manufacturing experts came together from more than 60 organizations—including from industry (e.g., Big Pharma, biotech, startups in stem cell and T-cell therapies, supply chain, and supporting automation technology companies), clinical Good Manufacturing Practice (GMP) facilities, academic research, government agencies, and private foundations. During these workshops, participants identified current cell manufacturing challenges and needs, identified and prioritized research and development activities that address these challenges, and defined the vision and mission of the NCMC. The distribution of participants based on organization type is presented in Figure 1.

The priority activities outlined in this roadmap will inform the initiatives of the NCMC, as well
as the cell manufacturing industry as a whole, academic researchers, public and private funding agencies, and policy makers. The ultimate vision of the NCMC is for the United States to maintain its global prowess as the leading developer of cell manufacturing technologies and manufacturer of cells and for the U.S. to be viewed as the chief authority on cell manufacturing standards and practices worldwide. To achieve this vision, NCMC will work to develop and mature technologies and infrastructure relevant to cell manufacturing; to facilitate regulation, commercialization, and adoption of emerging technologies by the cell manufacturing industry; and to build and train a skilled industry workforce that can sustain continuous industry progress.

### National Cell Manufacturing Consortium (NCMC) Vision

The United States establishes and maintains its global prowess as the leading developer of cell manufacturing technologies and manufacturer of cells and is viewed as the chief authority on cellular manufacturing standards and practices.

### Who Should Read this Roadmap?

This roadmap will be of use to a variety of individuals within and beyond the cell manufacturing community. It is not written solely for pharmaceutical or biotechnology companies, but rather for a range of stakeholders within industry, academia, and government who are critical to advancing this industry. Achieving large-scale, reproducible production of high-quality therapeutic cells at low cost will require a convergence science approach that brings together clinicians, cell biologists, and immunologists with a wide variety of engineers and scientists—not only bioengineers and chemical engineers who have been classically involved in biomanufacturing, but also electrical and mechanical engineers, computer and data scientists, systems biologists, chemists, physicists, and manufacturing and industrial engineers.

To realize large-scale cell manufacturing, industry and clinical Good Manufacturing Practice (GMP) centers must focus on the priority activities outlined in this roadmap to drive the development and implementation of advanced cell manufacturing technologies and techniques. Academic researchers must support these efforts by conducting the R&D necessary to bring these life-changing tools and techniques to market. Sensors and automation, big data analytics and machine learning, process engineering and plant design, and systems integration and instrumentation must all be an integral part of the fundamental national strategy to achieve success in industrial-scale cell manufacturing. To inform the efforts of industry scientists and academic researchers, physicians, biologists, and clinical scientists must provide the supporting knowledge and design parameters necessary to realize the therapies and treatments that will allow them to improve the lives of millions of people.

In the absence of regulatory buy-in, standardization, social buy-in, and insurance reimbursement, the promises of cell therapies and regenerative medicine will fail to reach their transformative potential. Government agencies, law makers, regulatory personnel, standards organizations, policy experts, the reimbursement industry, and private foundations must acknowledge the cell manufacturing industry’s areas of priority need, focusing resources in these areas and developing regulations and standards that can facilitate this industry’s accelerated growth.
Executive Summary

Advanced, large-scale manufacturing of high-quality cells has the potential to transform the healthcare industry, improving the health of millions of people while significantly growing the U.S. economy. A coordinated approach to developing and implementing next-generation cell manufacturing technologies is critical to realizing this impact and to securing the United States’ lead in this emerging field.
Over the past few decades, cell-based medical technologies have helped treat many patients with cancer, blood disorders, vision disorders, and other ailments. In 2012 alone, these products treated more than 160,000 patients.\(^1\) Though this relatively new industry has been growing significantly—with annual U.S. revenue above $1 billion—its potential is still far from being fully realized.

New and emerging cell-based healthcare products, such as cell therapies, engineered tissues, medical devices, and drug discovery and testing platforms, could help manage and even cure many conditions and diseases that are intractable, chronic, and even terminal today, including cancer, heart failure, paralysis from spinal cord injuries, and autoimmune disorders. Advanced cell-based technologies can help meet the needs of an aging population, accelerate recovery from injuries, and reduce the number of people on transplant lists—currently more than

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**What are Cell-Based Medical Technologies?**

This roadmap is focused on advancing the manufacturing of cells intended for use in final products, including the following:

**Cell Therapies** — the administration of live cells or genetically altered genes, often via blood transfusions, infusion, or bone marrow transplants, to a patient to replace live cells or repair damaged or diseased cells or tissues

*Emerging products and applications:*
  - Cell-based cancer vaccine for metastatic prostate disease
  - Spray-on cells for wound healing
  - T cell immunotherapy for cancers
  - Stem cell therapies for strokes, heart failure, autism, fibrosis, diabetes, and spinal cord injury

**Engineered Tissues** — growth of tissues, (e.g., bone, cartilage, skin, muscle, and organs) from live cells for implantation into a patient to restore, maintain, or improve tissue and organ function

*Emerging products and applications:*
  - Ocular, cardiovascular, and neurological tissue regeneration
  - Vascular grafts
  - Joint cartilage regeneration

**Medical Devices** — devices that measure and monitor cell function, some of which deliver physical, magnetic, electrical, optical, or chemical stimuli to cells to diagnose, control, treat, or prevent disease or to improve sub-optimal cell function

*Emerging products and applications:*
  - Hip implants
  - Disk repair
  - Neural probes

**Drug Discovery and Testing Platforms** — using live cells in pharmaceutical research to study diseases and suboptimal cell function and to test potential treatment compounds in the laboratory for safety and efficacy

*Emerging products and applications:*
  - Organ-on-a-chip models that simulate the activities of organs and organ systems

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Cell-based technologies could also advance screening platforms for predictive and personalized medicine, allowing earlier treatment of some diseases such as cancer and diabetes, and could facilitate the discovery of safer and more efficient drugs.

Though cells are the building blocks of all of these products, most U.S. investment in this field to date has neglected the advancement of cell manufacturing. Federal agencies—including the National Institutes of Health, Department of Defense, Department of Veterans Affairs, National Science Foundation, Food and Drug Administration, National Nuclear Security Administration, and National Institute of Standards and Technology—invested nearly $3 billion in regenerative medicine from 2012–2014, most of which was focused on basic and clinical research of new therapies. Bringing these new life-changing cell-based medical products to market critically depends on the large-scale, cost-effective, reproducible manufacturing of a variety of cell types.

Through a collaborative, strategic effort as called for in this roadmap and the support of public-private-philanthropic partnerships, the U.S. cell manufacturing industry can lead the advancement of cell manufacturing and enable the increased availability of innovative cell-based technologies. A dedicated translational effort and funding on the order of several hundred million dollars per year—or at least 10%–20% of investments in regenerative medicine—over the next 10 years would greatly accelerate this progress, maintaining the United States’ foothold in the industry and its contributions to the entire global cell manufacturing and cell-based products community.

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Definitions: Types of Cells

Cell manufacturing involves the production of a variety of cell types and their derivatives. Though there are commonalities in the manufacturing of each of these cell types, manufacturing processes must be tailored to each specific cell type. This report divides cell types and the activities needed to advance their manufacturing into the following three areas:

**Autologous**—cells harvested, expanded, and later administered to the same patient as a point-of-care cell-based medical product

**Allogeneic**—cells from a donor that are expanded and banked for use in cell-based medical products

**Pluripotent**—unspecialized cells capable of differentiating into a variety of cell types with specialized functions, including muscle cells, red blood cells, or cells of a particular organ
Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Strategy Through 2025

For the United States to maintain and secure its strong foothold in the dynamic cell-based technologies industry, multidisciplinary industry stakeholders—including researchers in the fields of biology, chemistry, and physics; equipment producers; cell and product manufacturers; and regulatory officials—must establish a collaborative U.S. cell manufacturing community. By capitalizing on existing expertise, technologies, and process knowledge, the community can streamline its efforts and accelerate progress toward large-scale, cost-effective, reproducible manufacturing of high-quality cells.

This roadmap offers a strategy to guide the cell manufacturing community’s efforts over the next 10 years. It combines focused research and development activities with initiatives designed to support and sustain the cell manufacturing industry. In addition to developing and implementing advanced technologies and techniques, the cell manufacturing community must strengthen the industry foundation needed to facilitate the advancement and market penetration of cell-based medical treatments. This strategy to enable large-scale, cost-effective, reproducible manufacturing of high-quality cells is depicted in Figure 2.

The activities included in this roadmap are designated with the cell type—autologous, allogeneic, and pluripotent for the purposes of this report—to which they are targeted, with some activities crosscutting the manufacturing of all of these cell types. The high-priority activities included in this strategy—those with the greatest potential impact on cell manufacturing industry advancement in the next 10 years—are included in Figure 3.

Develop and Implement Advanced Technologies and Techniques

Current cell manufacturing equipment and methods will not be able to meet the cell production scales needed to realize the potential of advanced medical treatments, devices, and diagnostics. To increase the scale and speed of cell production, the cell manufacturing community must collaborate on developing and maturing innovative technologies and techniques—including culture media and cell storage alternatives, sensors, process models, data analytics, and monitoring and tracking systems. Advancing technologies that can also improve quality assurance, reduce manufacturing and product costs, enhance manufacturing reproducibility and consistency, strengthen information technology security, and increase treatment efficacy will support long-term growth of the industry.

To accelerate technology development and implementation, manufacturers and researchers must work together to identify industry needs and optimize the cell manufacturing technologies and techniques with the greatest potential impact on industry operations. This close collaboration will also facilitate the implementation of these technologies across cell manufacturing facilities, accelerating the time it takes for technologies to move from the laboratory to commercial scale.

Strengthen the Industry Foundation

Beyond managing the technical aspects of cell processing, storage, and quality control, the cell manufacturing community must also
build a workforce and establish standards and regulations that can sustain long-term industry growth. An effective workforce needs to be capable of not only operating, but continuously improving next-generation cell manufacturing technologies and their associated techniques. At the same time, cell manufacturing standards and regulations must be put into place that encourage innovation and improve manufacturing quality across the value chain. These advances to cell manufacturing are a foundational component of enabling a more robust regenerative medicine supply chain.

Figure 2. Roadmap Strategy
Figure 3. Priority Roadmap Activities

<table>
<thead>
<tr>
<th>Type of cell:</th>
<th>Autologous</th>
<th>Allogeneic</th>
<th>Pluripotent</th>
<th>Crosscutting</th>
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**DEVELOP AND IMPLEMENT ADVANCED TECHNOLOGIES AND TECHNIQUES**

### Cell Processing

- **Separation Techniques**
  - Identify scalable methods for separation and purification

- **Culture Media Advances**
  - Develop and optimize inexpensive, chemically defined media and universal feeder systems free of animal cells and components

- **Cell Expansion Equipment**
  - Engineer bioreactors with increased capacity and integrated information technology systems that incorporate online monitoring and enable integrated feeds

- **Cell Expansion Equipment**
  - Develop automated, closed systems that allow for parallel manufacturing of multiple patient samples

- **Cell Expansion, Modification, and Differentiation Methods**
  - Develop scalable differentiation processes

- **Cell Expansion, Modification, and Differentiation Methods**
  - Identify method for low-cost, high-efficiency genetic modification that can engineer cells to elicit the desired response

### Cell Preservation, Distribution, and Handling

- **Product Tracking Systems**
  - Define methods to segregate and securely track products and patient information in a multiproduct manufacturing facility

- **Storage Infrastructure**
  - Develop infrastructure and methods to address the long-term storage of all types of manufactured cells

- **Advanced Cryopreservation Technologies**
  - Improve understanding of cell responses to cryopreservation and thawing interactions to inform process design

- **Alternative Preservation Technologies**
  - Identify shipping and storage alternatives to cryopreservation

### Process Monitoring and Quality Control

- **Cell Attribute Testing and Measurement Technologies**
  - Develop standardized high-throughput assays and surrogates to ensure cell-to-cell consistency in terms of phenotype, functionality, quality, and potency over a range of timeframes

- **Data Analytics**
  - Improve analytics for pattern recognition, critical quality attribute determination, and key performance parameter determination
### DEPLOY AND IMPLEMENT ADVANCED TECHNOLOGIES AND TECHNIQUES (CONT.)

<table>
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<tr>
<th>Process Monitoring and Quality Control (cont.)</th>
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<tr>
<td><strong>Data Management</strong></td>
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<tr>
<td>Identify all variables that impact the cost and viability of cell manufacturing processes</td>
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<tr>
<td><strong>Data Management</strong></td>
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<tr>
<td>Establish industry standards and specifications for consistently gathering and recording data</td>
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<tr>
<td><strong>Bioprocess Models</strong></td>
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<tr>
<td>Establish generalized bioprocess models and model scale-up to proposed commercial levels to identify process bottlenecks, cost drivers, and space and supply chain constraints</td>
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<tr>
<td><strong>Monitoring and Feedback Control Technologies</strong></td>
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<tr>
<td>Advance and integrate sensors that can non-destructively gather and transmit data</td>
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<tr>
<td><strong>Cell Attribute Testing and Measurement Technologies</strong></td>
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<tr>
<td>Develop reliable real-time, image-based, in-line analytical methods for small volumes that collect comprehensive data about the cells and media</td>
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<tr>
<td><strong>Bioprocess Models</strong></td>
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<tr>
<td>Evaluate various competitive upstream and downstream processing equipment and predict their impact on cost and manufacturability (quality is assumed equivalent)</td>
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<tr>
<td><strong>Cell Attribute Testing and Measurement Technologies</strong></td>
</tr>
<tr>
<td>Develop and validate all-in-one non-destructive rapid test method with sensors and imaging technologies for assessing critical quality attributes</td>
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<tr>
<td><strong>Data Management</strong></td>
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<tr>
<td>Develop or leverage systems that can integrate clinical data and allow for real-time visibility into relevant scheduling cues as well as data correlations to clinical outcome</td>
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### STRENGTHEN THE INDUSTRY FOUNDATION

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<th>Standardization and Regulatory Support</th>
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<tr>
<td><strong>Regulatory Strategy Development</strong></td>
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<tr>
<td>Form a working group to engage with Office of Cellular, Tissue and Gene Therapies, Office of the Director, on cell therapy policy issues</td>
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<tr>
<td><strong>Regulatory Strategy Development</strong></td>
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<tr>
<td>Engage with the U.S. Food and Drug Administration on issues of single-patient personalized medicine and regulatory requirements</td>
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<tr>
<td><strong>Product Quality Standards</strong></td>
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<tr>
<td>Establish reference materials for in-process and release assays</td>
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### STRENGTHEN THE INDUSTRY FOUNDATION (CONT.)

#### Standardization and Regulatory Support (cont.)

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<tr>
<td><strong>Product Quality Standards</strong> Establish quality-by-design principles for cell product manufacturing</td>
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<tr>
<td><strong>Product Quality Standards</strong> Develop guidelines regarding cell genetic stability and chromosomal aberrations</td>
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<tr>
<td><strong>Product Quality Standards</strong> Establish standards for acceptable levels of residuals and impurities in final products</td>
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#### Workforce Development

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<tr>
<td><strong>Higher Education</strong> Launch graduate and postdoctoral industry internships that include preparatory curriculum with instruction on industry skills for productivity, case studies of successful and failed processes and products, and rapidly changing guidance documents</td>
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<td><strong>Higher Education</strong> Create a university training model with continuous industrial engagement in areas of cell manufacturing knowledge, including logistics, revenue, intellectual property, and confidentiality</td>
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<td><strong>Higher Education</strong> Engage local community and technical colleges to help train the entry-level workforce in the skills that industry has identified as critical to advancing cell manufacturing</td>
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<tr>
<td><strong>Workforce Training</strong> Educate industry about data that should be routinely captured, stored, and analyzed, prioritizing data that is most critical for assessing product efficacy</td>
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<td><strong>Higher Education</strong> Pilot undergraduate internship or cooperative education program with preparatory courses</td>
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<tr>
<td><strong>Higher Education</strong> Institutionalize internship or cooperative education program for undergraduates</td>
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The Need for U.S. Investment in Cell Manufacturing

Investments in research and development of cell manufacturing technologies and processes, coupled with supporting initiatives to build a skilled workforce and develop industry standards and regulations, could enable the biomanufacturing community to meet intensifying market demands for new cell-based medical treatments. Ultimately, these initiatives will help secure the United States’ position as a global leader of state-of-the-art, life-changing therapies.

Large-scale cell manufacturing and the resulting increased commercialization of cell-based products will also accelerate the widespread achievement of several important national goals (outlined on page 9).

Securing U.S. Competitiveness in an Increasingly Global Market

The United States is currently at the forefront of biomedical research and technology development. International investments in this field, however, are quickly growing, and many countries throughout the world have established national centers to better compete in the growing global industry. Without comparable or greater U.S. investment in cell manufacturing, the United States will no longer be able to secure its lead in this potentially disruptive industry. An overview of some of the key centers currently in operation—including Cell Therapy Catapult (United Kingdom), the Cell Therapy Manufacturing Cooperative Research Centre (Australia), the Center for Commercialisation of Regenerative Medicine (Canada), and the Center for Regenerative Therapies Dresden (Germany)—is provided in the text box on page 10.

Recognizing the need for a focused cell manufacturing effort in the United States, more than 60 organizations—including from industry (e.g., Big Pharma, biotech, startups in stem cell and T-cell therapies, supply chain, and supporting automation technology companies), clinical GMP centers, academic research, government agencies, and private foundations—came together to develop this roadmap. Although U.S. progress can and will be made to address the activities outlined in this roadmap through individual research efforts, a more extensive and coordinated cell manufacturing community, supported by public-private-philanthropic partnerships, will be critical for maximizing U.S. cell manufacturing industry progress.
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Improved health and reduced disease burden
Large-scale cell manufacturing can help bring more effective treatments to market that address the underlying causes of many diseases and conditions rather than only managing their symptoms. These emerging and next-generation cell-based medical products could cure or significantly change the course of diseases, reducing the need for life-long treatments and ultimately improving the quality of life of millions of people.

Increased competitiveness of U.S. manufacturing
Currently, there are more than 700 companies, ranging from small and medium businesses to multinational corporations, focused on the research and development of cell-based medical products. Increased U.S. investment in cell manufacturing could grow the number of U.S. companies and jobs in this field, building a skilled workforce that can secure the United States’ lead in the emerging field of cell-based medical treatments.

Economic growth
Biotherapeutic companies currently generate nearly $1 billion in revenue from cell-based medical treatments. Large-scale cell manufacturing will enable the scaling up of existing and emerging cell-based products and allow new products to come to market, accelerating the path to growing the industry to a multi-billion-dollar global market in the next decade. The economic growth of the industry will benefit local economies as well, particularly as cell manufacturing expands throughout the United States.

More affordable healthcare
The United States spends nearly $3 trillion each year on healthcare. Many diseases currently require life-long care and management, creating a significant financial strain to consumers and the government over the course of patients’ lives. This economic burden could be reduced by the advancement of large-scale cell manufacturing and the resulting increased availability of cell-based medical treatments that can minimize the need for long-term management of diseases impacting the U.S. population.

Enhanced national security
The increased availability of novel cell-based medical treatments could enable faster and more effective treatment of military personnel and first responders. Large-scale U.S. cell manufacturing could also help to better accommodate surge demands for cell-based medical treatments in response to emergency incidents—including natural disasters, transportation accidents, exposure to hazardous materials, and terrorist attacks—while reducing the risk of supply disruptions from dependencies on overseas resources.

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International Investments in Cell Manufacturing*

The following international centers are focused on growing each individual nation’s contributions to the global cell manufacturing market. The United States must invest comparable or greater resources to establish and maintain its global prowess as the leading developer of cell manufacturing technologies and manufacturer of cells.

**Cell Therapy Catapult – United Kingdom (UK)**

The vision of Cell Therapy Catapult (CTC) is for “the UK to be a global leader in the development, delivery and commercialization of cell therapies, and a place where businesses can start, and confidently grow.” The CTC comprises industry, research, and regulatory institutions, who jointly move products into clinical trial; provide technical expertise and infrastructure to manufacture products and deliver them cost effectively; facilitate global and national opportunities for collaboration; and provide business grants and investment financing to advance new products and generate new business propositions. CTC operates on $15 million per year from the UK Technology Strategy Board and $31 million per year from industry and other partner funding.

**Cell Therapy Manufacturing Cooperative Research Centre – Australia**

The Cell Therapy Manufacturing Cooperative Research Centre (CRC) has a mission “to facilitate the cost-effective manufacture and rapid translation of cell therapies into clinical practice.” To this end, the CRC develops new treatments and new materials-based manufacturing technologies to treat conditions such as diabetes, chronic wounds, cardiovascular disease, and immune-mediated diseases. CRC comprises industry, research, and government institutions, and operates on a total budget of $43 million in cash and in-kind resources, including $15 million from the Australian Government.

**Center for Commercialisation of Regenerative Medicine – Canada**

The Center for Commercialisation of Regenerative Medicine (CCRM) is a consortium of industry members and research organizations that “supports the development of foundational technologies that accelerate the commercialization of stem cell- and biomaterials-based products and therapies.” CCRM conducts work in cell reprogramming and engineering, cell manufacturing, and biomaterials and devices, operating on a 2011–2016 budget of $12 million from the Networks of Centers of Excellence of Canada and $4.8 million from industry and academic partners.

**Center for Regenerative Therapies Dresden – Germany**

The Center for Regenerative Therapies Dresden (CRTD) aims to develop new regenerative therapies. CRTD comprises international and interdisciplinary research groups, who conduct basic and clinical research within four key research areas: hematology/immunology, diabetes, neurodegenerative diseases, and bone regeneration. The CRTD is funded by the German Research Foundation (DFG) as a DFG research center and as a Cluster of Excellence. As a Cluster of Excellence, CRTD receives $6.9 million in funding per year. CRTD scientists also raise third-party funds for their research. Additional funding details are not available.

*Center funding amounts have been converted to U.S. dollars based on October 14, 2015 exchange rates.
Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Technology Roadmap to 2025
Cell Processing

Cell processing—the growth of cells in an artificial environment outside of the human body—is a defining part of the cell manufacturing process. Each parameter of cell culturing, including the vessel, media, nutrients, and physicochemical environment, influences the properties that cells require to be effective therapeutically.
The development of new cell-based medical products will demand cell processing technologies and techniques capable of manufacturing cells in greater quantities at greater speeds. However, the materials, space, labor, and time requirements of current methods will prevent existing processes from meeting this growing demand.

To enable large-scale manufacturing of high-quality cells in the next 10 years, the cell manufacturing community must work together to develop, optimize, and implement more cost-effective and efficient cell processing technologies and techniques. Approaches that can also increase the consistency and reliability of cell processing could enhance the quality and efficacy of cell-based products.

**Current Challenges**

To realize large-scale, cost-effective, reproducible manufacturing of high-quality cells, the cell manufacturing community must work to overcome the cell processing challenges that follow.

**Linear nature of existing culture platforms**

Most current culture platforms (e.g., planar culture systems or feeder cells) are linear and require additional surface area to manufacture cells in greater quantities. The resulting space constraints, coupled with the substantial culture media and labor requirements of current systems, render existing culturing approaches economically impractical for commercial-scale manufacturing. Additionally, it is difficult to control nutrient gradients across these linear systems to achieve consistent cell characteristics and quality.

**Increased potential for contamination in open-culture settings**

In conventional research settings, the current process of dividing cell cultures to enable further proliferation is carried out in open systems where vessels are exposed to the surrounding environment. Every opening of a culture vessel poses the potential for contamination from molds, yeasts, viruses, mycoplasma, and other cell lines. The care taken to maintain sterile environments to reduce this risk is time- and labor-intensive, necessitating the need for innovative closed-system technologies that are sealed from the external environment.

**Difficulty understanding cell complexity**

The cell manufacturing community lacks sufficient understanding of the biology and emergent properties of human cells, particularly stem cells and immune cells. Understanding of human cells is further complicated by the fact that cells produced through cell manufacturing differ from those in the body. Because of the inherent complexity of cells, it is difficult to define the needed properties—or the mode of action—for cells to be useful therapeutically or the culture environments and differentiation processes necessary to manufacture cells with these properties.

**High cost, limited supply, and inconsistency of raw materials**

Culture media—including growth factors, nutrients, and reagents—are often the most expensive part of the cell manufacturing process. The high cost, as well as the limited supply and shelf life of some raw materials, will prevent existing culture platforms from meeting increased cell production demand. An additional complication is that some media components, particularly animal serums, have batch-to-batch variability, which can reduce cell property consistency and even contaminate cell products.
Inefficiency of cell separation methods

In many current cell processing systems, cells must be removed from the surface of culturing vessels and separated into new vessels with fresh growth medium for further propagation. When preparing cells for distribution, cells must also be separated from culture media, undifferentiated cells, and other particulates to achieve the cell purity needed for the end product. Current separation processes are inefficient and challenging, particularly because desired cells are often the same size as unwanted particles. Desired cells are also fragile and subject to shear, further adding to the complexity of cell separation.

Key Initiatives

Addressing these challenges will require coordinated efforts across the cell manufacturing community to develop, optimize, and implement advanced cell processing technologies and techniques. To realize the potential of large-scale, cost-effective, reproducible manufacturing of high-quality cells, the cell manufacturing community must collaborate on the following key cell processing initiatives: Screening and Selection Methods; Culture Media Advances; Cell Expansion Equipment; Cell Expansion, Modification, and Differentiation Methods; and Separation Techniques. Activities for each of these initiatives are provided in Figure 4, divided into near-term (2016–2018), mid-term (2019–2021), and long-term (2022–2025) time frames.

Screening and Selection Methods

The therapeutic effectiveness of cell-based treatments, devices, or diagnostic technologies demands the selection of cells with the desired properties for that specific medical product. Current processes for selecting viable, suitable cells can involve extensive trial and error, necessitating the development and optimization of highly automated cell screening and selection methods. Advanced approaches to donor and cell screening, including the use of more sophisticated assays and imaging technologies, could enable cell manufacturers to more quickly, efficiently, and accurately assess and select cells.

Culture Media Advances

To manufacture lot sizes with trillions of cells, the cell manufacturing community must advance non-linear culture formats, such as suspension cultures, that optimize cellular productivity. Without the need for substrates, microcarriers, or feeder cells, such culture systems could better utilize space, reduce labor requirements, and eliminate what is currently one of the primary cost drivers of cell manufacturing. The cell manufacturing community has the opportunity to develop more chemically defined media alternatives to reduce the risk of contamination from animal materials and overcome the limited availability of clinical-grade sera. Advanced cell culturing formats, lower-cost and more reliable media, and more precise cell passaging could reduce cell processing costs while also maximizing cell yield and quality.

Cell Expansion Equipment

To support the manufacturing of a variety of new cell-based technologies, next-generation cell expansion equipment must be able to accommodate varying lot sizes and parallel processing of different cell types. Seed trains and bioreactors with parallel processing capabilities could increase manufacturing throughput and shorten processing time, while distributing cost over multiple batches. Advanced cell expansion must also be highly automated and conducted in closed systems that can be monitored and maintained at defined physiochemical levels, resulting in cultures with comparable characteristics.
from batch to batch. Closed-system, parallel processing with increased automation is also critical to minimize error and contamination from human interaction with cell products.

**Cell Expansion, Modification, and Differentiation Methods**

To more accurately and efficiently differentiate cells with the desired characteristics for a cell-based medical product, the cell manufacturing community must increase its understanding of cell biology. Increased understanding of why cells do what they do—including how they respond to media and environmental conditions, the speed at which they double, and the optimum time to culture them—will enable increased control of cell properties. The industry could also reduce processing times and increase capacity by accelerating the biological speed of cell differentiation (e.g., with the use of complex cell cultures and epigenetics) or reducing cell doubling times. Increasing the speed of expansion and differentiation is particularly important for pluripotent stem cells, which can currently take several months to expand and differentiate, slowing the speed and quantity at which cell-based products are available.

**Separation Techniques**

The removal of viable cells from culture media, inactive products, undifferentiated cells, and other particulates is critical to the purity, quality, and safety of cell products. Development of advanced cell separation techniques, particularly for next-generation multi-parameter closed systems, is needed to reduce the labor requirements of both cell reseeding and cell expansion (e.g., detachment from microcarriers and substrates). More efficient separation technologies can also reduce the amount of media and space needed for cell processing.

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**Figure 4. Cell Processing Priority Activities**

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**Screening and Selection Methods**

- Establish standardized techniques for biopsies, including of induced pluripotent stem cells
- Standardize methods for selecting suitable induced pluripotent stem cell colonies
- Advance high-throughput image analysis and integrated data capture technology to assess morphology of colonies and inform selection of clones or embryoid bodies
- Establish a method for rapid donor screening (e.g., assay technology) for use early on in the culturing process to assess the viability and potency of cells and their suitability for process integration
- Collect and analyze upstream processing image data to automate clonal selection and remove subjectivity in decision-making
- Develop assays (e.g., measuring polymerase chain reaction [PCR] or cell surface markers) that test the potential for cells to form teratomas without the use of severe combined immunodeficiency mice
Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Technology Roadmap to 2025

Figure 4. Cell Processing Priority Activities (cont.)

<table>
<thead>
<tr>
<th>Type of cell:</th>
<th>Autologous</th>
<th>Allogeneic</th>
<th>Pluripotent</th>
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<tr>
<td><em>High-Priority Activities in Bold</em></td>
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Screening and Selection Methods (cont.)

- Conduct research into overcoming human leukocyte antigen matching to enable T-cell allogeneic therapies

Culture Media Advances

- Optimize existing microcarrier seeding and loading processes to increase cell density and reduce cost
- Define methods for growing autologous products in the absence of antibiotics
- Develop and optimize inexpensive, chemically defined media and universal feeder systems free of animal cells and components
- Eliminate need for feeder cells or uniform conditioned media and identify paracrine factors to increase understanding of cell functionality and facilitate increased process efficiency
- Produce a panel of quality assays to ensure serum consistency and assess safety
- Improve input material control to better understand the design space around culture parameters and lower-cost media
- Develop substrate- and microcarrier-free large-scale cultures of adherent cells

Cell Expansion Equipment

- Develop seed trains that require fewer steps to achieve cell amounts needed to seed the final bioreactor
- Develop scalable microcarrier and stir tank bioreactors that enable increased throughput
- Engineer bioreactors with increased capacity and integrated information technology systems that incorporate online monitoring and enable integrated feeds
- Develop automated, closed systems that allow for parallel manufacturing of multiple patient samples
### Cell Expansion Equipment (cont.)

- Generate devices that automate adherent cell cultures, including seed trains and expansion phase
- Extend holding times of final formulation to enable large lot sizes
- Develop tools for closed-system processing that eliminate the need for cleanroom space and permit manufacturing in non-classified space
- Create modular, flexible systems capable of producing several cell types simultaneously
- Achieve an integrated end-to-end automated parallel closed-system process
- Develop closed-system, non-manual, and efficient technology for automated tissue processing

### Cell Expansion, Modification, and Differentiation Methods

- Define the acceptable limits of population doubling, senescence, and exhaustion and identify ways to overcome these limits
- Develop a reagent and method for large-scale T-cell activation
- Develop scalable differentiation processes
- **Identify method for low-cost, high-efficiency genetic modification that can engineer cells to elicit the desired response**
- Advance closed-system gene delivery technology for transduction, screening, and selection
- Identify a method that can reduce the time needed to expand and differentiate pluripotent stem cells to 10%–20% of the current process time, which can take several months
- Improve understanding of the effects of environmental and media conditions
Figure 4. Cell Processing Priority Activities (cont.)

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<td>Crosscutting</td>
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</table>

### Cell Expansion, Modification, and Differentiation Methods (cont.)

- **Produce automated parallel transfection process**

- **Develop differentiation assay solutions based on the sensitivity of the assay or technology**

### Separation Techniques

- **Identify scalable methods for separation and purification**

- **Improve the software and imaging systems needed to automate visual inspection methods for distinguishing between cells and extraneous matter, including particulates and inactive products, reducing labor requirements and the cost of goods sold**

- **Improve purification methods and quality control tests for separating undifferentiated cells from differentiated cells to ensure quality and increase safety**

- **Characterize cell-surface interaction to design surfaces that allow for gentle detachment**

- **Engineer tangential flow systems for cell products**

- **Develop closed-system large-scale cell purification process and parallel cell purification system**

- **Design a co-culture system and separation method for feeder cells**

- **Develop high-efficiency automated graft fractionation technology**
Cell Preservation, Distribution, and Handling

The care taken to preserve, distribute, and handle cells is critical to cell quality. Current preservation methods, however, are unable to cost effectively ensure the stability of cells at large scales or for long periods of time.
As demand for cell-based medical products grows, reliable storage will be needed to preserve finite cell lines as well as cells that are manufactured in excess of immediate demand. Additionally, to expand the current cell distribution network, the cell manufacturing community must build capabilities to efficiently and cost effectively transport multiple cell types while tracking the workflow of each cell product.

To enable large-scale manufacturing of high-quality cells in the next 10 years, the cell manufacturing community must work together to develop, optimize, and implement more reliable and cost-effective cell preservation, distribution, and handling technologies and techniques. Lower-cost and more reliable approaches that better maintain cell viability and functionality and extend the shelf life of manufactured cells could facilitate the increased availability of high-quality cell-based medical products.

**Current Challenges**

To realize large-scale, cost-effective, reproducible manufacturing of high-quality cells, the cell manufacturing industry must work to overcome the cell preservation, distribution, and handling challenges that follow.

**High cost and complex logistics of distribution**

The distribution logistics and shipping schedules of cells, both fresh and frozen, are difficult to manage due to the short shelf lives of cells and requirements for carefully controlled environments. As a result, the current cost of cell product distribution is higher than that of the cost of cell manufacturing, particularly for autologous cells that require careful tracking. Shipping a single bag of bone marrow cells at the proper vapor phase, for example, can currently cost thousands of dollars.

**Difficulty scaling storage processes**

Current cell storage processes rely on cryopreservation and cold-chain-management equipment. Scaling up these processes is likely to increase incidents of transient warming that can be detrimental to cell quality and viability. Without process advances, the labor, materials, and facility requirements of these processes will also prove cost-prohibitive at larger scales.

**Difficulty maintaining cell characteristics during freezing and thawing**

During biopreservation, cell metabolic activity decreases and extracellular ice forms to protect cells. During this process, initiation of molecular stress responses and intracellular ice formation can also cause mechanical breakdown, membrane rupture, or other stresses that interfere with cell survival and recovery. The cell manufacturing industry, however, has limited understanding of cell viability and the functionality of various cell types following preservation and subsequent thawing, making it difficult to preserve cells effectively and consistently.

**Key Initiatives**

Addressing these challenges will require coordinated efforts across the cell manufacturing community to develop, optimize, and implement advanced cell preservation, distribution, and handling technologies and techniques. To realize the potential of large-scale, cost-effective, reproducible manufacturing of high-quality cells, the cell manufacturing community must collaborate on the following key cell preservation, distribution, and handling initiatives: Storage Infrastructure, Product Tracking Systems, Advanced Cryopreservation Technologies, and Alternative Preservation
Technologies. Activities for each of these initiatives are provided in Figure 5, divided into near-term (2016–2018), mid-term (2019–2021), and long-term (2022–2025) time frames.

Storage Infrastructure

Cell banks, which typically store cells using cryopreservation, maintain valuable backup supplies of cells. Such cell storage helps to mitigate losses of cell integrity from genetic drift, contamination, and processing equipment failures, ensuring the long-term stability of cell lines with the desired critical quality attributes. To establish cell supplies that can meet growing demand for cell-based medical products, the cell manufacturing community must build a more robust and reliable storage infrastructure that accommodates larger quantities of a greater number of cell types.

Product Tracking Systems

The cell manufacturing industry needs to implement a robust, efficient, automated, real-time bioinformatics-based tracking procedure that records each processing step, tool, and raw material (e.g., nutrient, biologic) used in the manufacturing of a cell product. Tracking the chain of custody could inform process adjustments that can optimize manufacturing processes to facilitate the increased safety, quality, and efficacy of cell-based products. Additionally, a Health Insurance Portability and Accountability Act (HIPAA)-compliant process in which every bag or vial of cells contains a chip with the associated product information will ensure that the correct cells are administered to the correct patient while also keeping patient information secure.

Advanced Cryopreservation Technologies

To enable large-scale cell manufacturing, the industry needs advanced cryopreservation processes that can cost effectively preserve a greater variety of cells in larger volumes. The cell manufacturing community must work to develop highly automated cryopreservation technologies that facilitate more precise control of freezing and thawing. Increased understanding of the impact of this process on cells could also reduce cell stress and maximize recovery, improve homogeneity of frozen batches, and extend product shelf life to reduce manufacturing cost and waste.

Alternative Preservation Technologies

Some cell types (e.g., skin cells) do not maintain potency after being frozen, necessitating cell preservation and storage alternatives to cryopreservation. The cell manufacturing community must collaborate on advancing alternative storage methods (e.g., room-storage, hypothermic, and freeze-drying methods) for various batch sizes and cell types that can better maintain cell quality and functionality. Identifying and advancing such alternatives to cryopreservation could increase the flexibility, reliability, and cost effectiveness of cell storage.
Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Technology Roadmap to 2025

Figure 5. Cell Preservation, Distribution, and Handling Priority Activities

<table>
<thead>
<tr>
<th>Storage Infrastructure</th>
<th>Type of cell: Autologous</th>
<th>Allogeneic</th>
<th>Pluripotent</th>
<th>Crosscutting</th>
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<tbody>
<tr>
<td>Launch induced pluripotent stem cell and human embryonic stem cell banking initiative</td>
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<tr>
<td>Determine largest master cell bank size possible based on required cell numbers and doses</td>
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<tr>
<td>Define criteria for master cell bank stability over time and develop stability-indicating assays</td>
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<tr>
<td>Develop infrastructure and methods to address the long-term storage of all types of manufactured cells</td>
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<tr>
<th>Product Tracking Systems</th>
<th>Type of cell: Autologous</th>
<th>Allogeneic</th>
<th>Pluripotent</th>
<th>Crosscutting</th>
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<tbody>
<tr>
<td>Define methods to segregate and securely track products and patient information in a multiproduct manufacturing facility</td>
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<tr>
<td>Generate electronic batch records and develop raw material control for numerous processes in parallel</td>
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<tr>
<td>Develop reusable distribution solutions such as easy-to-sterilize capsules that transmit location and record critical environmental encounters</td>
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<tr>
<td>Develop and integrate an automated reading device (e.g., bar coded or radio-frequency identification [RFID]) to gather data inputs from different sources and points during the workflow—including at manufacturing and clinical sites—and enable 100 percent chain-of-custody recording</td>
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<tr>
<th>Advanced Cryopreservation Technologies</th>
<th>Type of cell: Autologous</th>
<th>Allogeneic</th>
<th>Pluripotent</th>
<th>Crosscutting</th>
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<tbody>
<tr>
<td>Develop processes for large-scale (i.e., number of units, unit volume) cell cryopreservation that improve cell quality, functionality, and batch homogeneity</td>
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<tr>
<td>Identify intermediate cryopreservation steps to reduce potential risks from transient warming</td>
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<tr>
<td>Improve understanding of cell responses to cryopreservation and thawing interactions to inform process design</td>
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### Advanced Cryopreservation Technologies (cont.)

<table>
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<tr>
<th>Activity</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Develop an automated storage process that includes cell harvest, vialing, transfer to controlled-rate freezers, and transfer to liquid nitrogen tanks for cryopreservation</td>
<td>near (2016–2018)</td>
</tr>
<tr>
<td>Discover new cryoprotectants and high-throughput methods to identify and implement them</td>
<td>mid (2019–2021)</td>
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### Alternative Preservation Technologies

<table>
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<tr>
<th>Activity</th>
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<tr>
<td>Identify better containers (e.g., smart or reusable packaging) for cell preservation to decrease shipping costs</td>
<td>near (2016–2018)</td>
</tr>
<tr>
<td>Identify potential areas for process streamlining or biopreservation to extend holding or process times of cells during downstream processing</td>
<td>near (2016–2018)</td>
</tr>
<tr>
<td>Conduct a study to assess cell potency and viability, particularly as a result of transient warming, compared with the cost of storage using liquid nitrogen, ultradep freezer (-80°C), warmer-temperature cell bank storage, and smaller-batch controlled-rate freezing</td>
<td>near (2016–2018)</td>
</tr>
<tr>
<td>Engineer end-user-friendly formulation that allows for higher-temperature storage</td>
<td>near (2016–2018)</td>
</tr>
<tr>
<td>Identify shipping and storage alternatives to cryopreservation</td>
<td>near (2016–2018)</td>
</tr>
<tr>
<td>Develop room-temperature cell preservation method</td>
<td>near (2016–2018)</td>
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Process Monitoring and Quality Control

A single process alteration during cell manufacturing could yield cells with properties that deviate from those required for a specific cell-based medical product. More consistent and reliable cell manufacturing processes will be critical to ensure the quality of manufactured cells, particularly as demand for these cells grows.
Sophisticated process simulation, monitoring, and feedback control technologies—such as models, assays, and sensors—could improve the ability to control cell manufacturing processes and increase understanding of the impact of process variations. These advances could also facilitate real-time decision-making and potentially even automated process corrections that would significantly improve process robustness and efficiency.

To enable large-scale manufacturing of high-quality cells in the next 10 years, the cell manufacturing community must work together to develop, optimize, and implement more cost-effective and accurate real-time process monitoring and quality control technologies and techniques. Process monitoring and quality control approaches that can more quickly characterize cells and optimize process parameters could improve the affordability and reliability of cell-based products.

Current Challenges

To realize large-scale, cost-effective, reproducible manufacturing of high-quality cells, the cell manufacturing community must work to overcome the process monitoring and quality control challenges that follow.

Lack of readily available, robust data

Many individual cell manufacturing companies are reluctant to share data due to the competitive nature of the industry. As a result, the cell manufacturing community currently lacks readily available, robust data about cell manufacturing processes and cell products. Without accessible, accurate data, it will be challenging to accelerate process understanding and precisely tailor processes to cost effectively manufacture large quantities of high-quality cells.

Inability to assess cell viability and characteristics in real time

Alterations to any critical cell characteristics—those that make cells therapeutically active—will render cells useless for their intended application. Yet, the cell manufacturing industry currently lacks sufficient tools to measure cell biomarkers, characterize cells, determine potency, and assess purity in real time to prevent the production of unusable cell products. Cost-effective, large-scale manufacturing will not be possible without the ability to detect and consequently mitigate inconsistencies or issues in cell processing.

Difficulty identifying and containing the spread of contaminants

One of the primary ways to detect contaminants in cell cultures is through visually inspecting cultures for cloudiness, thin films, or other signs that a culture has been compromised. Using this approach, however, it may take several days after cultures are infected to identify an issue. Other contaminants, including viruses and mycoplasmas, are even more difficult to detect until they achieve much higher densities. By the time contamination is identified, it may have spread more widely throughout the facility, altering cell behavior and function and ruining entire cell lots.

Insufficient models for bioprocessing

While some manufacturing parameters can be measured and controlled, it is difficult to predict the impact of manufacturing conditions on cell behavior given the variability in both cells and patients. Current models are, therefore, inherently incapable of simulating all relevant bioprocess parameters. The cell manufacturing
community will need sophisticated models and established testing procedures to conduct accelerated stability testing and accurately predict the impact of process variations, including scale-up to larger bioreactors, on cell performance and product cost.

Key Initiatives

Addressing these challenges will require coordinated efforts across the cell manufacturing community to develop, optimize, and implement advanced process monitoring and quality control technologies and techniques. To realize the potential of large-scale, cost-effective, reproducible manufacturing of high-quality cells, the cell manufacturing community must collaborate on the following key process monitoring and control initiatives: Monitoring and Feedback Control Technologies, Cell Attribute Testing and Measurement Technologies, Data Analytics, Data Management, and Bioprocess Models. Activities for each of these initiatives are provided in Figure 6, divided into near-term (2016–2018), mid-term (2019–2021), and long-term (2022–2025) time frames.

Monitoring and Feedback Control Technologies

Monitoring and feedback control technologies could help cell manufacturers more quickly identify and correct processing issues that impact cell quality, potency, purity, or safety. To improve process controls, the cell manufacturing community must collaborate on technologies such as sensors, assays, and imaging systems that can more accurately measure processing conditions like pH, dissolved oxygen, and metabolite accumulation. These technologies can also be leveraged to detect contaminants earlier than current methods, enabling cell manufacturers to contain contamination more quickly to reduce its costly repercussions. In addition to developing better ways to capture process data, the cell manufacturing community must build capabilities for transmitting this data. Developing a centralized, easy-to-operate communications network could facilitate real-time, and even automatic, process adjustments and enable parallel processing of multiple cell types with varying process requirements.

Cell Attribute Testing and Measurement Technologies

To release cells for distribution, cell manufacturers must define cell critical quality attributes (CQAs)—including cell identity, purity, potency, and safety—that can affect the primary mode of action. The ability to quickly and accurately assess CQAs will require advanced technologies such as assays, sensors, and imaging technologies that can rapidly characterize cells in real time without damaging the cells and reducing the manufacturing yield. The resulting comprehensive in-process cell data would provide the cell manufacturing community with insight into process deficiencies and help predict cell function and efficacy. Ultimately, this ability to ensure cell-to-cell consistency could enable large-scale manufacturing and increase the affordability of end products.

Data Analytics

To maximize the value of technologies that capture cell manufacturing data, the cell manufacturing industry needs robust systems that can quickly synthesize and interpret this data. Advanced in-line data analytics software and statistical algorithms could correlate data from different sources throughout the manufacturing process and draw meaningful conclusions in real time. This in-process data analysis could facilitate improved decision-making or even self-correcting systems that can increase the cost effectiveness, throughput, and efficiency of cell manufacturing processes.
and ultimately drive the manufacturing of higher-quality cells.

**Data Management**

Accessibility of robust data, from raw material sourcing to clinical implementation, is critical to better predict and optimize cell manufacturing processes. To maximize the value of existing data, the cell manufacturing community must integrate disparate data from across different companies and databases into more centralized data management systems. Increasing the comprehensiveness of industry data will also require the systematic generation and standardized recording of data for other variables that impact manufacturing costs and cell viability. Systems that can capture multiple data streams from across the manufacturing process and extract data from different sources throughout the cell manufacturing industry will be pivotal in increasing the robustness of data available for modeling and process controls as well as enhancing chain of custody.

**Bioprocess Models**

Advanced bioprocess models—including supply chain and cost models—could help the cell manufacturing community more efficiently improve processes and optimize properties of manufactured cells. These models must account for all the factors that could impact the properties and performance of cells and cell products, including the stochastic variability of cells and the inherent variability of cell functionality and cell therapy patients. Models could also more accurately predict manufacturing conditions (e.g., gas exchange, reagent buildups, shear forces, and temperature variations) in larger-scale reactors to reduce the cost and time associated with trial-and-error approaches to scale-up. As models improve, the cell manufacturing community could use them to evaluate the impact of new and emerging technologies and fine-tune manufacturing and supply chain efficiency of more complex cell manufacturing processes.

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![Figure 6. Process Monitoring and Quality Control Priority Activities](image)

**Monitoring and Feedback Control Technologies**

- Establish a working group to identify critical manufacturing steps that impact safety, purity, and potency and define acceptable ranges of process variability
- Apply smart manufacturing sensors and controls to monitor process conditions (e.g., exposure to high temperatures and humidity) that could impact cell quality
- **Advance and integrate sensors that can non-destructively gather and transmit data**
- Produce a single-use sensor for critical process parameters and control points
- Build an easy-to-operate, automated central controller that can accommodate multiple units for parallel processing
- Develop sensor that triggers the biomaterial to change color to demonstrate progress of cultures

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Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Technology Roadmap to 2025
Figure 6. Process Monitoring and Quality Control Priority Activities (cont.)

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<thead>
<tr>
<th>Monitoring and Feedback Control Technologies (cont.)</th>
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<tbody>
<tr>
<td>Refine process monitoring software, including optical, metabolic, and dynamic scheduling software, based on feedback and design space</td>
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<td>Develop a signaling device to alert operators to the possibility of cell environmental conditions that could affect cell activity</td>
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<td>Develop sensors that can be embedded in the matrix to visualize cells grown on a microcarrier</td>
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<tr>
<td>Develop real-time critical quality attribute monitoring systems (e.g., with advanced sensor technology) that adjust process parameters to drive cell populations to a functional state</td>
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<table>
<thead>
<tr>
<th>Cell Attribute Testing and Measurement Technologies</th>
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<tr>
<td>Develop standardized high-throughput assays and surrogates to ensure cell-to-cell consistency in terms of phenotype, functionality, quality, and potency over a range of timeframes</td>
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<tr>
<td>Advance cell health and impurity monitoring, including establishing criteria and shear sensitivity of serum-free grown cells</td>
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<tr>
<td>Generate a potency assay (i.e., reliable surrogate assay) that rapidly tests secretion molecules</td>
</tr>
<tr>
<td>Develop reliable real-time, image-based, in-line analytical methods for small volumes that collect comprehensive data about the cells and media (e.g., activity base, morphology, phenotype, metabolism)</td>
</tr>
<tr>
<td>Develop online, in-process characterization tools for predicting cell function</td>
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<tr>
<td>Produce rapid multi-parameter cytometry technology with low cell or tissue requirements to facilitate real-time decision-making during in-process and final product release testing</td>
</tr>
<tr>
<td>Develop technologies for phenotypic tracking that are amenable to emergent, staged manufacturing processes for pluripotent cells</td>
</tr>
<tr>
<td>Develop non-leachable in-situ sensors that transmit data remotely on metabolome, secretome, etc.</td>
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</table>
Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Technology Roadmap to 2025

<table>
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<tr>
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### Cell Attribute Testing and Measurement Technologies (cont.)

- Develop and validate all-in-one non-destructive rapid test method with sensors and imaging technologies (e.g., cell-permeable probes) for assessing critical quality attributes, including sample identity, purity, potency (e.g., cytokines, cell number), metabolites, and sterility.

- Develop modular final product tests (e.g., rapid biological tests, potency characterization).

- Establish cell-specific sensor platform with microcarrier plug-and-play options for different cell types.

### Data Analytics

- Improve analytics for pattern recognition, critical quality attribute determination, and key performance parameter determination.

- Identify optimized cell sampling plan, such as automated, closed-system in-process sampling processes, to enable in-line analytics.

- Generate multivariate statistics that will enable online monitoring of metabolic profiles to control and minimize media usage.

- Improve analytics for safety assays, differentiation, and vector residuals.

- Improve detection technologies by developing advanced analytics, devices, image processing, and learning systems.

- Automate analytics for product release, including gene editing, human leukocyte antigen typing, sterility/mycoplasma removal, and tissue compatibility testing.

- Automate imaging software and correlates for advanced pattern recognition.

### Data Management

- Identify all variables that impact the cost and viability of cell manufacturing processes, including materials availability and cost, equipment scalability and maintenance, labor requirements, facility grade and design, quality control and regulatory compliance, processing and shipping logistics, yield (i.e., batch size and batch number per year) and failure rate; and processing speed.
### Data Management (cont.)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establish industry standards and specifications for consistently</td>
<td>near (2016–2018)</td>
</tr>
<tr>
<td>gathering and recording data (from donor, through process, to delivery),</td>
<td>mid (2019–2021)</td>
</tr>
<tr>
<td>engaging NIST to establish the standards along with tools and technology</td>
<td>long (2022–2025)</td>
</tr>
<tr>
<td>providers to integrate them</td>
<td></td>
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<tr>
<td>Develop a generic process map (one each for autologous, allogenic, and</td>
<td></td>
</tr>
<tr>
<td>pluripotent cell types) of all data sources, process inputs and outputs,</td>
<td></td>
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<tr>
<td>and software types and languages across the workflow (i.e., from raw</td>
<td></td>
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<tr>
<td>materials sourcing to clinical trials), and use these maps to conduct a</td>
<td></td>
</tr>
<tr>
<td>gap analysis of cell manufacturing data and supporting information</td>
<td></td>
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<tr>
<td>technology</td>
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<tr>
<td>Define standard methodologies for flow cytometry methods for cell</td>
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<tr>
<td>surface marker expression (e.g., via a publication or position paper)</td>
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</tr>
<tr>
<td>Develop a software or technology solution (e.g., sensor-enabled technology that integrates with software) to easily extract data about equipment use, maintenance, calibration, and critical process parameters from electronic batch records, electronic notebooks, and other types of electronic databases (e.g., laboratory information management systems)</td>
<td>mid (2019–2021)</td>
</tr>
<tr>
<td>Develop or leverage systems that can integrate clinical data (e.g., trial, quality control in-process, final product release, post-marketing) and allow for real-time visibility into relevant scheduling cues as well as data correlations to clinical outcome</td>
<td>mid (2019–2021)</td>
</tr>
<tr>
<td>Engineer a single-source software solution that captures and synthesizes multiple data streams from equipment used at various parts of the process and integrates analysis of this data (e.g., with artificial intelligence, using algorithms) to identify trends and inform decision-making and continuous data mining</td>
<td>mid (2019–2021)</td>
</tr>
<tr>
<td>Develop a flexible and accessible data management system that allows for capture of different and variable types of data (automated and/or manual) from raw materials sourcing and testing; and integrates and communicates with existing software solutions (e.g., manufacturing execution systems [MES], enterprise resource planning [ERP])</td>
<td>long (2022–2025)</td>
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</table>

### Bioprocess Models

<table>
<thead>
<tr>
<th>Activity</th>
<th>Timeframe</th>
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<tbody>
<tr>
<td>Establish generalized bioprocess models and model scale-up to proposed commercial levels to identify process bottlenecks, cost drivers, and space and supply chain constraints</td>
<td></td>
</tr>
<tr>
<td>• Autologous: T-cell, dendritic cells, or mesenchymal stem cells</td>
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<tr>
<td>• Allogeneic: human mesenchymal stem cells, chondrocyte, or tissue-engineered trachea or blood vessels</td>
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<tr>
<td>• Pluripotent: human embryonic or induced pluripotent stem cells related to cardio, neurological, or diabetes</td>
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</table>
Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Technology Roadmap to 2025

**Figure 6. Process Monitoring and Quality Control Priority Activities (cont.)**

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<tbody>
<tr>
<td>Bioprocess Models (cont.)</td>
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<tr>
<td>Identify, evaluate, and modify bioprocess modeling software suite (e.g., with chemical engineering characterization, fluid dynamics modeling, and cell shear modeling) for modeling cell therapy and regenerative medicine manufacturing processes—including the impact of scale-up on material handling, quality control, and inventory/shipping</td>
<td><img src="image" alt="Crosscutting" /></td>
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<tr>
<td>Develop supply chain models that include non-destructive testing of final products for sterility, potency, etc. to reduce waste due to shelf-life expirations</td>
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<tr>
<td>Model bioreactor mechanical force, pH, carbon dioxide, and oxygen levels for pluripotent stem cell manufacturing</td>
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<td><img src="image" alt="Crosscutting" /></td>
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<tr>
<td>Evaluate various competitive upstream and downstream processing equipment and predict their impact on cost and manufacturability (quality is assumed equivalent)</td>
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<td><img src="image" alt="Crosscutting" /></td>
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<tr>
<td>Improve or expand on in-vitro predictive models (e.g., cell matrix measurement) for cell characterization and performance</td>
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<tr>
<td>Establish methods for using validated bioprocess models to quickly troubleshoot manufacturing failures and drive corrective and preventative actions</td>
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<td><img src="image" alt="Crosscutting" /></td>
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<tr>
<td>Build models that include more complicated regenerative medicine manufacturing processes and technologies, including tissue engineering, whole organ engineering, and cell-based combination products</td>
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<tr>
<td>Develop models and assays needed to conduct accelerated shelf-life stability studies</td>
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<td><img src="image" alt="Crosscutting" /></td>
<td><img src="image" alt="Crosscutting" /></td>
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<td><img src="image" alt="Crosscutting" /></td>
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<tr>
<td>Identify ways to redesign Good Manufacturing Practice (GMP) facilities to better accommodate therapies and products whose production is highly individualized</td>
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<td><img src="image" alt="Crosscutting" /></td>
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<td><img src="image" alt="Crosscutting" /></td>
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<tr>
<td>Assess tracking and trending of actual commercial manufacturing process data, accounting for business parameters such as margin and reimbursement rate, to evaluate the impact of scrap and identify ways to fine-tune manufacturing and supply chain processes</td>
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</tr>
</tbody>
</table>
Standardization and Regulatory Support

Due to the complexity and constantly evolving nature of the cell manufacturing industry, there is currently a lack of consensus on industry standards. As a result, seemingly similar populations of cells manufactured at different locations could have significantly different properties and modes of action, limiting the industry’s ability to predict cell behavior and treatment efficacy.
To improve the consistency and quality of manufactured cells and cell-based products, the cell manufacturing industry must work with regulatory agencies, including the U.S. Food and Drug Administration and other regulators across the global cell manufacturing industry, to define standards and regulations for cell manufacturing processes and cell products. Establishing standards and regulations—including for raw materials, testing procedures, manufacturing processes, and cell product handling—is critical to drive the development of innovative cell products and efficiently move them to commercialization and clinical use.

Current Challenges

To realize large-scale, cost-effective, reproducible manufacturing of high-quality cells, the cell manufacturing community must work to overcome the standardization and regulatory challenges that follow.

Difficulty defining the products of biological processes

In many cases, the cell itself is the product, but cells can also be vehicles to the synthesis of other products, including exosomes, antibodies, vaccines, and cytokines. Regulatory issues are further complicated in the case of combination therapies and other modalities with products that include both regular cells and genetically modified cells or other sophisticated systems. Because of this complexity, it is challenging to develop useful standards and regulations with specific parameters for a given cell type or product while still allowing further innovation.

Limited support for innovation built into industry standards

To accelerate the growth of cell manufacturing, the regulatory framework must evolve with major industry advances to support long-term technology innovation. Current U.S. cell manufacturing regulations differ from those in other countries, and some industry companies find that U.S. regulations put a greater burden on process and technology innovation. These regulatory differences make it difficult to efficiently move products from early development to commercialization and clinical use, which could impact the United States’ ability to maintain its lead in the global cell manufacturing industry.

Lack of product consistency across the supply chain

Due to concerns about product consistency across the supply chain, many of today’s cell manufacturers acquire critical raw materials and equipment from sole source vendors. This dependency increases the risk of supply interruptions and could limit manufacturing throughput and scale, possibly preventing patients from receiving effective and reliable treatments in a timely manner.

Key Initiatives

To address these challenges and realize the potential of large-scale, cost-effective, reproducible manufacturing of high-quality cells, the cell manufacturing community must collaborate on the following standardization and regulatory support initiatives: Regulatory Strategy Development, Supply Chain Consistency, and Product Quality Standards. Activities for each of these initiatives are provided in Figure 7, divided into near-term (2016–2018), mid-term (2019–2021), and long-term (2022–2025) time frames.

Regulatory Strategy Development

Regulations that account for the unique characteristics of cell manufacturing are critical to accelerate innovation of next-generation cell therapies, engineered tissues, medical devices, and drug discovery and testing.
platforms. The cell manufacturing industry must coordinate with regulatory agencies—
including with the Office of Cellular, Tissue and Gene Therapies (OCTGT); U.S. Food and
Drug Administration; Centers for Medicare and Medicaid Services (CMS); and the International
Conference on Harmonisation—to formulate a strategy for developing and harmonizing

cell manufacturing regulations. Keeping these agencies informed about emerging
technologies and techniques will help the cell manufacturing community advocate
for regulations that can continuously drive industry advances.

Supply Chain Consistency

Developing supply chain standards and metrics would help the cell manufacturing industry
increase the consistency of materials and process conditions that can impact cell critical

quality attributes. To ensure the reliability and quality of raw materials from different
suppliers, the industry should establish reference or calibration materials, particularly
as the supplier base expands to meet the

raw material and supply requirements of the

growing cell manufacturing industry. Because
manufacturing processes define cell properties,
the cell manufacturing industry must also
mitigate variations in environmental conditions
by developing standards for manufacturing
procedures that could impact the quality of
manufactured cells, including facility clean
room requirements and aseptic techniques to
prevent contamination.

Product Quality Standards

Improved product consistency could allow
the cell manufacturing community to more
accurately predict patient responses to cell-

based products. Increasing standardization
of assays and inspection methods for
product release and developing reference
standards for various cell types could help
improve consistency of manufactured cells
across companies and facilities. Additionally,
purity standards could reduce the amount
of inactive product and residuals in final
products, increasing the quality and safety of
cell-based products.

Figure 7. Standardization and Regulatory Support

<table>
<thead>
<tr>
<th>*High-Priority</th>
<th>Type</th>
<th>Autologous</th>
<th>Allogeneic</th>
<th>Pluripotent</th>
<th>Crosscutting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities in Bold</td>
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</tr>
</tbody>
</table>

Regulatory Strategy Development

- Form a working group to engage with Office of Cellular, Tissue and Gene Therapies (OCTGT), Office of the Director, on cell therapy policy issues

- Engage with the U.S. Food and Drug Administration (FDA) on issues of single-patient personalized medicine and regulatory requirements (e.g., synthetic DNA using patient’s gene sequence and viral vector delivery)

- Establish a working group, including FDA and the Centers for Medicare & Medicaid Services (CMS), to address third-party payer issues

- Establish a working group to define the regulatory pathway for cellular products through the FDA—addressing their unique challenges and requirements—and develop regulatory plan tools (e.g., templates, checklists, and limited population studies)
Figure 7. Standardization and Regulatory Support (cont.)

*High-Priority Activities in Bold

|---------------|------------|-----------|-------------|--------------|------------------|------------------|------------------|

**Regulatory Strategy Development (cont.)**

- Identify differences between smaller-scale autologous and larger-scale allogeneic manufacturing processes that would affect regulatory interactions
- Engage the International Conference on Harmonisation (ICH) to change Drug Substance to Drug Product in the Common Technical Document, Module 3 for investigational new drugs (INDs)

**Supply Chain Consistency**

- Develop ICH guidance with cell harvesting, processing, banking, testing, and administration standards for cell manufacturers
- Clarify definitions (e.g., serum free, xeno-free, chemically defined) regarding media composition
- Establish standards with FDA and the European Medicines Agency (EMA) for clean room requirements for different manufacturing platforms and processing devices (e.g., closed vs. open, welders)
- Establish waste handling procedures for large volumes
- Establish metrics for comparing tissue and blood processing practices across manufacturers and companies
- Define and standardize the optimal supply chain design
- Establish regulatory standards to ensure consistency of raw materials (e.g., serums) from different suppliers, reducing dependency on sole source providers

**Product Quality Standards**

- Establish reference materials for in-process and release assays
- Establish quality-by-design principles for cell product manufacturing
- Develop guidelines regarding cell genetic stability and chromosomal aberrations (i.e., pass/fail)
Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Technology Roadmap to 2025
Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Technology Roadmap to 2025
Workforce Development

Realizing and capitalizing on the benefits of advanced technologies and techniques depends on a highly skilled, multidisciplinary cell manufacturing workforce—with expertise in areas including biological science, engineering, computational modeling, physics, chemistry, mathematics, and statistics.
To strengthen the current workforce, the cell manufacturing community must collaborate with universities and continuing education programs to develop structured training frameworks. Such programs will help attract new talent to the industry and will provide the current workforce with the skills needed to efficiently operate and further improve advanced cell manufacturing technologies and techniques. Additionally, by fostering stronger partnerships across companies, disciplines, and industry segments, the cell manufacturing community can leverage existing expertise to further grow the skillsets, capabilities, and knowledge necessary to meet increasing demand for cell-based medical products.

Current Challenges

To realize large-scale, cost-effective, reproducible manufacturing of high-quality cells, the cell manufacturing community must work to overcome the workforce development challenges that follow.

Inadequate cell manufacturing education programs

Because cell manufacturing is a relatively new multidisciplinary field, there is a lack of robust curricula focused specifically on the field. The constantly evolving nature of the industry also makes it difficult to ensure the relevance and comprehensiveness of undergraduate, masters, doctoral/post-doctoral, and continuing education training programs, limiting the cell manufacturing workforce’s ability to maximize value from these programs.

Limited workforce diversity

The current cell manufacturing community does not have sufficiently broad expertise in fields outside of cell biology, including engineering, computational modeling, physics, chemistry, mathematics, and statistics, with the potential to greatly increase the understanding and efficiency of cell manufacturing processes. The industry also has a limited number of specialists with proficiency in quality and regulatory affairs and in infrastructure protection to move cell manufacturing to commercialization and clinical application.

Key Initiatives

To address these challenges and realize the potential of large-scale, cost-effective, reproducible manufacturing of high-quality cells, the cell manufacturing community must collaborate on the following workforce development initiatives: Higher Education, Workforce Training, and Cross-Industry Collaboration. Activities for each of these initiatives are provided in Figure 8, divided into near-term (2016–2018), mid-term (2019–2021), and long-term (2022–2025) time frames.

Higher Education

To grow the future workforce, the cell manufacturing community must invest in higher education activities that attract new graduates to the field and provide them with the skills necessary to sustain industry innovation. It will be critical for educators to continuously engage with industry to inform education programs, updating training content as new technologies, techniques, and regulations emerge. Industry engagement will also ensure that research conducted through undergraduate, graduate, and postdoctoral coursework has industry implications, and will help foster the relationships needed between universities and industry to provide students with hands-on, practical industry internships.

Workforce Training

The cell manufacturing community must conduct frequent workforce training on emerging topic areas, industry procedures, and cell manufacturing techniques and
technologies to provide the workforce with the knowledge and expertise necessary to implement new manufacturing approaches. Additionally, to ensure that manufacturing knowledge is current across the industry, the cell manufacturing community must formalize a mechanism for transferring legacy knowledge to new members of the expanding workforce. Building a highly skilled workforce could increase cell manufacturing productivity and efficiency, reduce workforce errors, and improve the consistency and quality of manufactured cells and cell-based medical products.

Cross-Industry Collaboration

To expand the cell manufacturing knowledgebase, the cell manufacturing community must foster stronger partnerships across companies, disciplines, and industry segments. Leveraging expertise and promoting idea exchange from outside of the current cell manufacturing community—including from existing consortia and the additive manufacturing and biotechnology industries—could help the cell manufacturing industry more efficiently and effectively overcome the current challenges of cell manufacturing.

Figure 8. Workforce Development Priority Activities

<table>
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<tr>
<th>Activities in Bold</th>
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<tbody>
<tr>
<td>Type of cell:</td>
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<tr>
<td>Autologous</td>
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<tr>
<td>Allogeneic</td>
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<tr>
<td>Pluripotent</td>
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<tr>
<td>Crosscutting</td>
</tr>
<tr>
<td>near (2016–2018)</td>
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<tr>
<td>mid (2019–2021)</td>
</tr>
<tr>
<td>long (2022–2025)</td>
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</tbody>
</table>

**Higher Education**

- Launch graduate and postdoctoral industry internships that include preparatory curriculum with instruction on industry skills for productivity (e.g., how to keep a laboratory notebook, how to manage intellectual property), case studies of successful and failed processes and products, and rapidly changing guidance documents such as those from the U.S. Food and Drug Administration (FDA)

- Create a university training model with continuous industrial engagement (e.g., survey industry on needed skills and knowledge gaps) in areas of cell manufacturing knowledge, including logistics, revenue, intellectual property, and confidentiality

- Engage local community and technical colleges to help train the entry-level workforce in the skills that industry has identified as critical to advancing cell manufacturing

- Build global awareness on challenges and opportunities in cell therapies through coursework and internships, including industry case studies on global regulatory issues (e.g., picking best trial country) and ethical considerations on how cell therapies are viewed or allowed in various countries

- Start planning inter-institutional training programs, including policies and logistics, that involve industry

- Pilot undergraduate internship or cooperative education program with preparatory courses
Figure 8. Workforce Development Priority Activities (cont.)

<table>
<thead>
<tr>
<th>High-Priority Activities in Bold</th>
<th>Type of cell:</th>
<th>Autologous</th>
<th>Allogeneic</th>
<th>Pluripotent</th>
<th>Crosscutting</th>
</tr>
</thead>
</table>

Higher Education (cont.)

- Implement responsive programs that address identified knowledge gaps in cell biomanufacturing and engage the appropriate instructors across disciplines (e.g., business, regulatory, and intellectual property)
- Implement inter-institutional training programs at graduate level
- Institutionalize internship or cooperative education program for undergraduates
- Implement inter–institutional training program at undergraduate level
- Institutionalize responsive educational programs that address identified knowledge gaps

Workforce Training

- Educate industry (e.g., through a white paper) about data that should be routinely captured (both automatically and manually), stored, and analyzed, prioritizing data that is most critical for assessing product efficacy
- Formalize a mechanism for transferring legacy knowledge to the younger workforce and facilitate interactions between the existing and emerging workforce through an existing or new professional society
- Build a cell-therapy-centric software workforce, including programming, computer intelligence, and software engineers, that extends beyond bioinformatics and cultivates a role for “cell therapy industrial engineers”
- Launch a massive open online course (MOOC) short course to train manufacturing personnel on emerging cell biomanufacturing topics to increase personnel qualifications

Cross-Industry Collaboration

- Engage biotherapeutic manufacturers to understand how modeling has been utilized in protein production and how tools have evolved over time
- Collaborate with FDA’s Mesenchymal Stem Cells Consortium
### Cross-Industry Collaboration (cont.)

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<tr>
<td>Gather data and input from industries outside the cell therapy industry to develop new technologies and bring system modeling tools to the cell manufacturing industry</td>
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<tr>
<td>Benchmark methodology from other emerging technology areas (e.g., 3D printing) to rapidly create new standards</td>
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<tr>
<td>Engage with thought leaders in the biotechnology industry to explore novel technologies for cell therapy manufacturing</td>
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<tr>
<td>Develop a shared testing and demonstration facility (e.g., pilot plant) for prototyping processes and operational parameters</td>
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The Path Forward

By combining focused research and development activities with initiatives designed to support and sustain the cell manufacturing industry, the cell manufacturing community can facilitate the advancement and market penetration of next-generation cell-based medical products and support the long-term growth and global competitiveness of the U.S. cell manufacturing industry.
Execution of the priority activities within this roadmap will be led by the National Cell Manufacturing Consortium (NCMC), an industry-driven effort aimed at establishing a collaborative public-private partnership between researchers, equipment producers, cell and product manufacturers, regulatory officials, and other relevant stakeholders. This community will accelerate growth of the U.S. cell manufacturing industry more so than individuals or small groups could accomplish working independently. By implementing the priority activities outlined in this roadmap, NCMC can fulfill its mission to develop and mature technologies and infrastructure relevant to cell manufacturing; to facilitate regulation, commercialization, and adoption of emerging technologies by the cell manufacturing industry; and to build and train a skilled industry workforce.

Though NCMC will be operated, in part, through monetary and in-kind support from its members, additional or matched external or federal funding would multiply the impact of the consortium’s efforts and ability to pursue a greater number of priority activities in this roadmap. A dedicated translational effort and funding on the order of several hundred million dollars per year for the next 10 years would greatly accelerate U.S. cell manufacturing progress and advance the United States as a global leader of state-of-the-art, life-changing therapies, engineered tissues, medical devices, and drug discovery and testing platforms. Such investments in research and development, coupled with supporting initiatives to build a skilled workforce and develop industry standards and regulations, are critical for enabling the biomanufacturing community to meet intensifying market demands—and potentially grow the industry to a multi-billion-dollar global market in the next decade. 

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**National Cell Manufacturing Consortium (NCMC) Vision**

The United States establishes and maintains its global prowess as the leading developer of cell manufacturing technologies and manufacturer of cells and is viewed as the chief authority on cellular manufacturing standards and practices.

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Appendices

Appendix A: Acronyms and Abbreviations
Appendix B: Roadmap Contributors
## Appendix A: Acronyms and Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMTech</td>
<td>NIST Advanced Manufacturing Technology Consortia program</td>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>CCRM</td>
<td>Center for Commercialisation of Regenerative Medicine</td>
<td>GRA</td>
<td>Georgia Research Alliance</td>
</tr>
<tr>
<td>CMS</td>
<td>Centers for Medicare &amp; Medicaid Services</td>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
</tr>
<tr>
<td>CRC</td>
<td>Cooperative Research Center for Cell Therapy Manufacturing</td>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>CRTD</td>
<td>Center for Regenerative Therapies Dresden</td>
<td>IND</td>
<td>investigational new drugs</td>
</tr>
<tr>
<td>CTC</td>
<td>Cell Therapy Catapult</td>
<td>MES</td>
<td>manufacturing execution systems</td>
</tr>
<tr>
<td>CQA</td>
<td>critical quality attribute</td>
<td>MOOC</td>
<td>massive open online course</td>
</tr>
<tr>
<td>DFG</td>
<td>Deutsche Forschungsgemeinschaft (German Research Foundation)</td>
<td>NIST</td>
<td>National Institute of Standards and Technology</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
<td>OCTGT</td>
<td>Office of Cellular, Tissue and Gene Therapies</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>ERP</td>
<td>enterprise resource planning</td>
<td>R&amp;D</td>
<td>research and development</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
<td>RFID</td>
<td>radio-frequency identification</td>
</tr>
<tr>
<td>Georgia Tech</td>
<td>Georgia Institute of Technology</td>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
</tbody>
</table>
# Appendix B: Roadmap Contributors

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