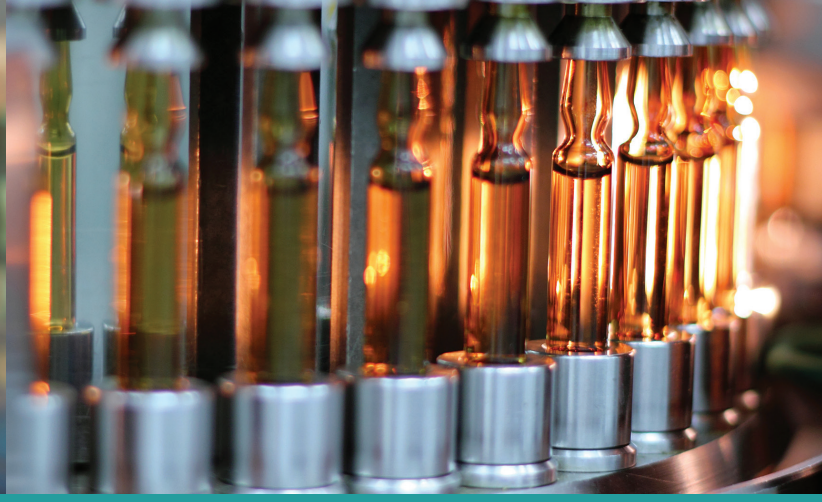

NIMBL

The National Institute for Innovation in Manufacturing Biopharmaceuticals

Gene Therapy Roadmap

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1.0 Executive Summary

The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) launched a technical roadmap process in 2017 to serve the needs of the biopharmaceutical manufacturing community in the US and worldwide. Subject matter experts representing major biopharmaceutical manufacturers, equipment vendors, suppliers, academic institutions, federal agencies and non-profits participated in a series of in-depth discussions focused on the technical needs and manufacturing challenges associated with biopharmaceutical products. These products are increasingly important for the treatment of patients with chronic and deadly diseases. We are grateful for the time that individuals (from both NIIMBL member and non-member organizations) contributed to this activity.

The topics for this roadmap process were chosen to complement other technology roadmaps for biopharmaceutical processing that were recently published or are in progress. At a visioning conference held in November 2017, it was decided the first NIIMBL roadmaps would focus on three areas: vaccines, antibody-drug conjugates and bi-specific antibodies, and gene therapy. Many individuals contributed to this effort, facilitated by BioPhorum and NIIMBL personnel, and we believe that the resulting roadmaps set the stage for numerous technical and process development efforts in the future. We look forward to NIIMBL's next set of roadmapping activities starting in late 2018.

Gene therapy is an emerging area of therapeutics with the potential for curative treatment. Advances in genomics, gene-editing methodologies, immunology and drug delivery technologies are driving a revolution in healthcare. This field is aimed at tackling the world's most grievous illnesses by correcting genetic defects, enhancing cellular and tissue function, and improving production of cellular products or generating novel screening targets for drug discovery.

Despite the rapid growth of gene therapy, several limitations remain relating to the ability to manufacture consistently and analyze the necessary therapeutic components, e.g. viral vectors, commonly used by many contemporary gene therapy innovators. Additionally, the need to produce ever-increasing amounts of these vectors to meet patient demand continues to put pressure on manufacturers. It should be noted that significant research is also underway in non-viral vector development; such vectors will be addressed in greater detail in future editions of this roadmap.

This NIIMBL roadmap on viral vector-based gene therapy provides a vision of the future of gene-level therapies and addresses the worldwide market trends and business drivers that influence manufacturing best practices for these emerging biotherapeutics. This roadmap has been constructed with an initial emphasis on the key unit operations common to many of the viral vector gene therapy processes currently being utilized at different scales. The roadmap also proposes some potential solutions to existing and anticipated production barriers.

Numerous issues are covered, including the production of the plasmid and host cell raw materials, the viral vector production process, rapid analytical methods, process optimization and control, knowledge transfer, regulatory science and standards development. Most of these issues span the entire production process, including upstream and downstream processing, and final drug product formulation. Finally, there is a discussion on workforce development needs, including the skills and knowledge base required for the future of biopharmaceutical manufacturing of these important classes of drugs. As with all of the NIIMBL roadmaps, the writing team has worked collaboratively to connect its efforts to complementary areas in other roadmaps.

The key conclusions and recommendations from this roadmap are:

1. **starting materials:** consistent, large-scale plasmid production and purification are central to the development of the genetic material required for gene therapy. Current plasmid production processes are limited in terms of production capability. Enhanced capability is required for improved supply chains for gene therapy
2. **upstream processing:** many current viral vector processes still employ adherent cell culture systems. Significant optimization, including use of suspension-based cultures, is needed to improve overall batch productivity and consistency
3. **formulation/stability and fill/finish:** many *ex vivo* viruses are inherently unstable for a number of reasons and work should be done to improve their robustness, preferably through optimized formulation
4. **analytics:** many of the contemporary analytical methods used to evaluate product yield, potency and purity lack the specificity and precision needed to ensure robust batch-to-batch product quality. New in-line and off-line technologies should be developed and integrated into gene therapy processing
5. **facilities:** due to the unique nature of viral vector processing (in particular, scale and safety considerations), solutions will be needed to allow for the flexibility and aseptic capabilities required for multiple products
6. **regulatory sciences:** early engagement with global regulators is needed to improve product consistency and quality, and help to ensure the smooth passage from early stage (Investigational New Drug) to commercial stage (Biologics License Applications) operations
7. **workforce:** there is a significant need for cross-disciplinary training to support gene therapy technology transfer and manufacturing operations. Ongoing collaboration and communication between gene therapy pioneers, subject matter experts and educators are critical to ensure tomorrow's workforce is prepared.

2.0 Introduction and background

2.1 Introduction

Gene therapy is a promising area of therapeutics with the potential to provide curative treatments to patients suffering from various genetic disorders. Advances in gene-correcting tools and drug delivery technologies are driving a revolution in healthcare. As of late 2017, there were over 3,000 clinical trials ongoing or completed worldwide and this number is rising quickly rapidly [1]. Despite the rapid growth of gene therapy, several limitations remain with regarding our ability to robustly manufacture the necessary therapeutic components, including the critical viral and non-viral delivery vehicles (termed vectors) and the ability to efficiently produce increasingly larger volumes of finished product. As a result, this acknowledged limitation within the overall drug supply chain will likely restrict the growth, and consequently curtail adoption, of many vector-driven, gene therapy treatment opportunities.

The complexity of developing gene therapy biopharmaceuticals, along with the breadth of modalities, creates significant challenges for the industry. For example, several different viral vector systems are used in variable frequencies by gene therapy manufacturers including (but not limited to) recombinant adeno-associated viruses (numerous serotypes), lentivirus, retrovirus, adenovirus and herpes simplex virus. In addition to the different vectors used, the significant variations in manufacturing processes adopted across the industry add to the overall complexity.

2.2 Background

Gene therapy is the administration of genetic material to modify or manipulate the expression of a gene product or to alter the biological properties of living cells for therapeutic use. Gene therapies can work in several mechanisms [2], as shown in Figure 1 and listed below:

- replacing a disease-causing gene with a healthy copy of the gene
- inactivating a disease-causing gene that is not functioning properly
- introducing a new or modified gene into the body to help treat a disease.

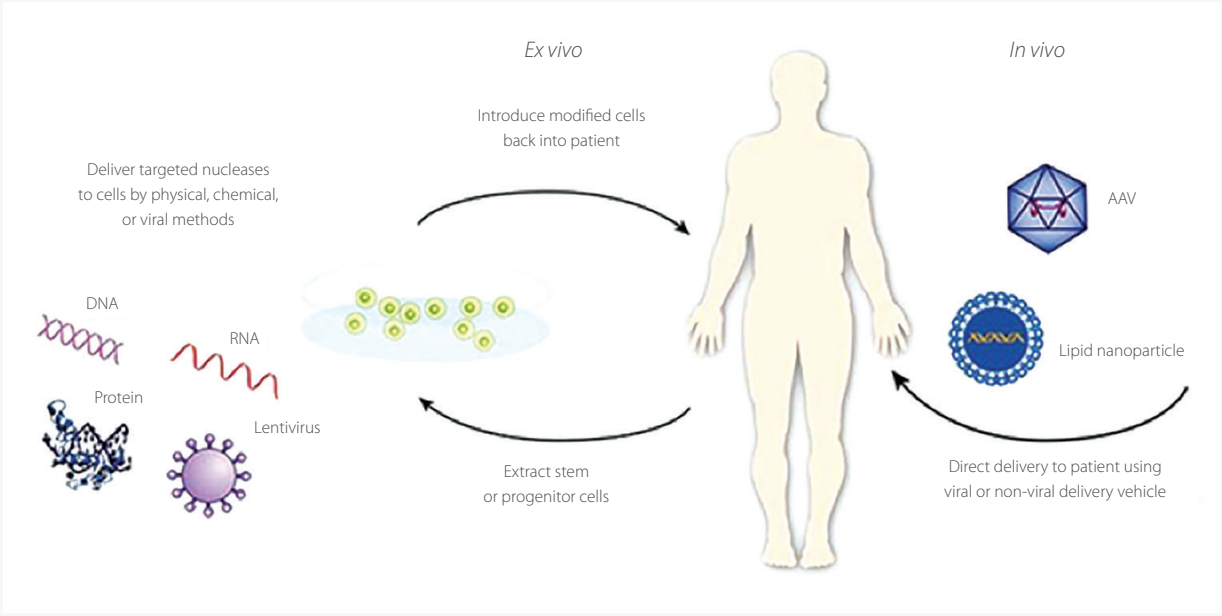
Gene therapy products are being studied to treat illnesses including cancer, genetic diseases and infectious diseases. There are a variety of gene therapy products available including:

- **plasmid DNA:** circular DNA molecules that can be genetically engineered to carry therapeutic genes, including a gene of interest (GOI), into human cells directly or using a suitable vector
- **viral vectors:** viruses have a natural ability to deliver genetic material into cells and therefore some gene therapy products are derived from viruses. Once viruses have been modified to remove their ability to cause an infectious disease, these modified viruses can be used as vectors to carry therapeutic genes into human cells
- **bacterial vectors:** bacteria can be modified to prevent them from causing an infectious disease and then used as vectors to carry therapeutic genes into human tissues
- **human gene-editing technology:** the goals of gene editing are to disrupt harmful genes or to repair mutated genes
- **patient-derived cellular gene therapy products:** cells are removed from the patient, genetically modified (often using a viral vector) and then returned to the patient.

Transfect HEK293T cells

Collect supernatant

Figure 1: Simplified illustration of mechanisms of action for in vivo and ex vivo gene therapy applications using viral and non-viral vectors for delivery to patients [2]



2.3 Vision and scope

It would be difficult for any single roadmap to comprehensively examine each of the myriad vector/production process combinations. Therefore, the authors have generalized the content when necessary but have been specific where possible.

2.3.1 Vision

The authors of this document believe the future state of biomanufacturing for gene therapy can be transformed by collaboratively addressing the highest priority needs. It is expected that process improvements will arise through these collaborations leading to improved manufacturing process productivity. In turn, this may also lead to the development of 'platform' or templated processes, resulting in reduced process variability and increased alignment across the whole industry. These advances will help ensure biomanufacturers of gene therapy products will be able to meet the extensive future demand of these truly promising therapies. Lastly, the authors recognize the need for improved early education and engagement to create a gene therapy workforce that rivals that of more traditional biologics processing.

2.3.2 Scope

This document is intended as a reference for the current state of viral vector bioprocessing. The authors provide assessments of the key industry needs, coupled with basic research at universities which will need to mature in the coming years to ensure gene therapy reaches its unique therapeutic potential and therefore benefit patients. The roadmap is focused on the gaps in enabling manufacturing technology that must be overcome to produce gene therapy products in a 'fully industrialized' manner. An existing technology cell therapy roadmap [3] published in 2016 by the National Cell Manufacturing Consortium, led by the Georgia Research Alliance and funded through National Institute of Standards and Technology, Advanced Manufacturing Technology (AmTech), allows this Gene Therapy Roadmap to focus on the manufacturing process for the construction and production of the gene vector, upstream of the manufacturing process. The authors of this roadmap recognize that various modalities, such as non-viral delivery mechanisms, may present disparate manufacturing challenges. However, given the contemporary predominance of viral vector-based gene delivery, the authors have decided to limit the content of this roadmap to these processes. Non-viral and direct delivery methods will likely be addressed in future editions of this roadmap.

As with most of the processes or components discussed in this roadmap, the authors recognize that while additional vector production systems (e.g. baculovirus/insect cell lines) are currently being employed by gene therapy producers, such approaches constitute a small fraction of the overall viral vector production landscape. Thus, the combination of a plasmid transfection/HEK-293 'upstream' production system will be the primary focus of this roadmap.

2.4 Market trends and business drivers

2.4.1 Market trends

Ongoing, evolving and emerging trends in the external environment beyond the control of a business entity have a profound impact on business strategies and plans. Many social, economic, technical and political trends are individually and collectively prompting growth in gene therapy approaches to healthcare. Gene therapy offers the potential for reduced total healthcare costs and societal benefits through one-time/curative treatments. A number of these trends are described in Table 1. While these external trends are not unique to gene therapy, the tools and technologies being developed are enabling previously unmet needs to be addressed. A more detailed review of this area is available in the BioPhorum Biomanufacturing Technology Roadmap [4].

Table 1: Gene Therapy Roadmap – key external trends

Socioeconomic	
Demographics	Cancer and other mono-genetic diseases are becoming more addressable
Healthcare costs	Gene therapy is extremely expensive but is potentially curative and can be performed in a 'one and done' manner. Therefore the drive is to reduce total manufacturing costs
Healthcare insurance	Lower total care costs offered by prevention and cure can increase coverage and treatment availability
Research funding	Reduced government funding for basic research is reducing innovation
Orphan legislation and fast-track regulatory pathways	High unmet needs have provided an accelerated pathway to approval, making this an attractive space for investment
Technology	
Gene-level therapy	Precise gene-editing tools offer the potential for *in vitro* and *in vivo* repair
'Big data' analytics	Biological databases are identifying novel therapeutic targets
Single-use systems	Engineered and customizable forms and assemblies utilizing plastics and new materials are enabling complex, miniaturized closed systems

2.4.2 Business drivers

Commercial entities direct their investment and operational activities to change key business metrics, which have a strong relationship to business effectiveness. Key business drivers can often be traced to a strategy focused on differentiation, cost or market leadership. Standard biomanufacturing business drivers apply to gene therapy such as; first-in-class therapies being rewarded with a larger market share and orphan legislation allowing for market exclusivity (for a finite period) for first-to-market therapies. Manufacturers strive for cost control measures, such as increased efficiency, improve profitability and the ability to compete in the marketplace. Novel drivers are generated from the potential for gene therapy to be curative, approaches can differentiate in therapeutic outcomes to patients.

Some examples of key business drivers for gene therapy are listed in Table 2

Table 2: Gene Therapy Roadmap – business drivers

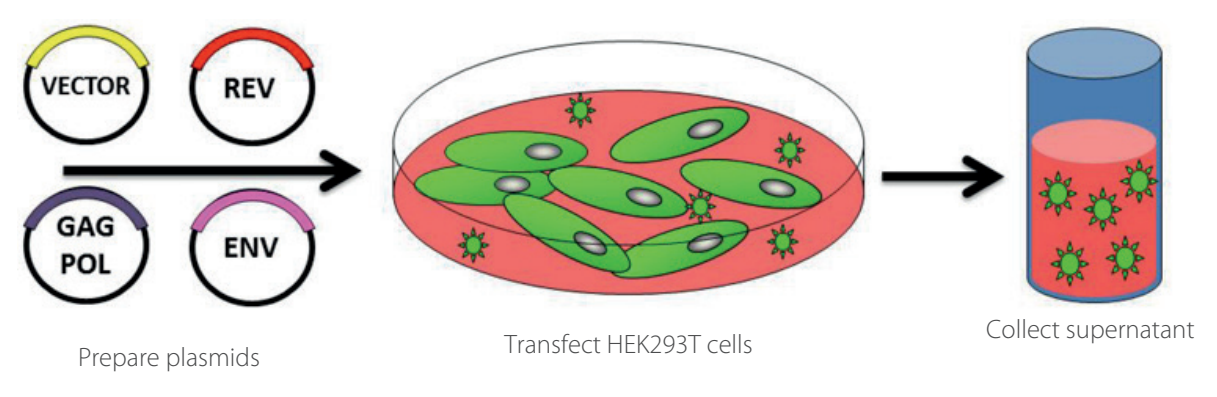
Cost and quality
Critical reagents and starting materials are high-cost and volume-limiting
Low productivity and failed lots increase unit costs
Extensive testing to ensure product quality and consistency increases production costs
Impurities negatively impact on product safety
Platform processes that can be implemented in multiple product facilities
Complexity of qualifying standards results in variable product quality
Speed and flexibility
Complex process development results in delays to market
Lack of modular/multi-product facilities
Lack of experienced Contract Manufacturing Organizations

3.0 Future needs, challenges and potential solutions

This section covers facets of virus production from the generation of critical starting materials to the purification and analytical techniques used to establish product quality. The manufacture of viral vector biologics is inherently complex and involves several highly specialized processes to arrive at a substance that is both safe and effective [5]. While each of the major gene therapy production components (e.g. upstream, downstream, analytics) differs significantly, they do maintain a single common trait; each employs a tool or set of tools that could benefit from significant optimization.

For example, many current viral vector-based gene therapy bioprocesses rely on 'transient' transfection to deliver the critical genes needed for viral construction to a host cell. These genes are often isolated in plasmids. Once transfected, the host cell will generate and assemble the virus needed to eventually deliver its own genetic payload to a patient's cells. This is a complicated process by which a large number of cells in a culture receive a 'cocktail' of genetic material, often distributed across several packaging plasmids as well as one containing the therapeutic GOI (see Figure 2). Alternatively, the genetic material can be delivered using a viral vector into the producer cell line.

Figure 2: Simplified host cell transfection process illustrating the use of multiple plasmids to produce a therapeutic viral vector



A potential solution to the transfection problem involves the engineering and use of stable producer cell lines, wherein the cells are hard-coded with the genes needed to produce the necessary viral components and the therapeutic GOI, without the need for an external plasmid addition step. Literature searches confirm that significant efforts are ongoing to design stable producer cell lines for several predominant viral vector systems. Nevertheless, to date, there are few examples of highly specialized stable cell lines. Regardless, the pursuit of such stable cell lines is underway in earnest across the gene therapy landscape and is discussed in greater detail in section 3.1.

Likewise, downstream purification unit operations use many of the same tools as those used for recombinant protein purification (e.g. column chromatography and forward, tangential flow filtration (TFF)), but have not been optimized for virus production. Finally, many of the analytical testing methods used to confirm product potency and purity tend to be extremely low throughout, less reproducible and labor intensive.

The following sections summarize many of these challenges and provide some detail around potential near-term solutions (over the next 2–3 years) as well as some aspirational approaches that will take longer to develop and implement. We have divided the biomanufacturing components into two segments; plasmids and host cell banks as critical starting materials, and the viral production process.

3.1 Production of cell, plasmid and recombinant viral banks

Before transfection of the host cells with the required number of plasmids, additional bioprocesses are needed to generate and purify the plasmids, and clone and isolate the suitable host cell bank that will serve as the engine for vector production. As expected, these bioprocesses are not trivial. This section provides several examples of how current techniques for the creation of these critical starting materials could potentially be improved.

3.1.1 Plasmid production

The majority of viral vector production systems use plasmid DNA to carry critical viral packing genes and the GOI to a cell that will make the actual vector. Plasmid production is a complicated procedure whereby the necessary vector packaging and GOI genetic sequences are created recombinantly and amplified through a microbial (e.g. E. coli) fermentation process. Once expressed and confirmed, the plasmid DNA must be harvested and further purified to exacting standards to ensure the resulting material is free of product- and process-related impurities. The plasmid DNA must then pass a battery of safety tests before being released for clinical and/or commercial use. Table 3 summarizes some of the current needs and challenges associated with this complex process as well as potential solutions and the generalized timelines for their development and/or implementation.

Plasmids manufactured in a multi-use facility with shared equipment (such as bioreactors, centrifuges and columns) can be contaminated with previously manufactured products. The US Food and Drug Administration (FDA) promotes adherence to the principles of current good manufacturing practices (cGMP) and testing for the presence of other contaminating plasmids in plasmid preparations.

3.1.2 Host cell bank production

The creation of a suitable host cell bank is a difficult and time-consuming process. The cell type most commonly used for transient transfection vector production processes is the mammalian line commonly referred to as HEK-293 and HEK-293T. The parent cells of these lines were originally harvested from a human embryonic kidney, with the latter containing the addition of a protein referred to as a large T-antigen on the cell surface. The majority of first-generation viral vector production processes use a suboptimal adherent version of HEK-293. However, the FDA suggests HEK-293T cells should not be used for manufacturing adeno-associated virus (AAV) vectors for gene therapy. The suggestion relates to the fact that the HEK-293T cells contain the DNA sequence of the SV40 large T-antigen, which is an oncogene and may be co-packaged into recombinant AAV products, potentially inducing tumors in the recipients. The use of HEK-293 cells inherently limits the scale-up of viral production to the number of two-dimensional cell adherence vessels that are capable of being processed [6].

These processes also tend to be manual, non-automated, more susceptible to contamination and extremely limited based on the need for an ever-increasing surface area for cell attachment. These traits make first-generation systems extremely challenging for large-scale production. As a result, there remains a strong desire among manufacturers to move away from adherent cell cultures and into suspension cultures, which are now state-of-the-art among biologics producers. Table 3 includes a section dedicated to the current state of cell-line production as well as the movement towards second- and even third-generation cell culture systems along with predictions of what it will take to achieve these advances in the coming years.

See Tables 3 and 4 for a list of needs, challenges and potential solutions relating to the production of plasmids host cells.

Table 3: Plasmid production – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Consistent large-scale production					Productivity and failed lots, unit cost
Challenge	Current *E. coli* expression system is limited					
Potential solution	Develop a higher-yielding plasmid production platform					
						
Need	Recovery of large plasmid DNA					Manufacturing frequency, lot-to-lot variability
Challenge	High-yield recovery from genomic DNA					
Potential solution	New chromatographic media					
						
Disruptive technology	Revolutionary separation technologies					
						
Need	Separation technology that achieves >95% purity of plasmid DNA					Productivity and failed lots, unit cost
Challenge	Increase yield of plasmid DNA and separation from genomic DNA and other process-related impurities					
Potential solution	Robust single-use ion exchange chromatography designed for plasmid DNA; single-use bioreactors					
						
Need	Plasmid DNA free of impurities					Manufacturing frequency. Lot-to-lot variability. Cost
Challenge	Non-bacteria-based plasmid DNA production					
Potential solution	Mini-circle DNA					
						
Disruptive technology	Highly selective enzymatic treatment					
						

Manufacturing Readiness Level

Research Development Manufacturing

Table 4: Host cell creation, production and banking – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Better clone-selection techniques					Cost and productivity. Lot-to-lot variability
Challenge	Current techniques may not identify the highest producers					
Potential solution	High-throughput screening to identify the highest producers					
						
Disruptive technology	A unique and highly specific biomarker that also serves as a selection marker					
						
Need	Enhanced transfection capability					Productivity and failed lots, unit cost
Challenge	Current transfection technology is non-optimized to achieve maximum virus production					
Potential solution	Improved 'design of experiment' approach for transfection efficiency; high-throughput screening technologies					
						
Disruptive technology	New cell lines developed that have enhanced transfection efficiency					
						
Need	Suspension-adapted cell cultures					Productivity and failed lots, unit cost
Challenge	Adherent cells have low productivity; equipment and labor intensive and expensive					
Potential solution	Develop suspension HEK-293 cell line or other suitable hosts					
						
Disruptive technology	Single-use technology					
						
Need	General purpose cell line with viral packaging components					Productivity and failed lots, unit cost
Challenge	Targeted integration of packaging components into host cell genome					
Potential solution	Increase co-transfection efficiency					
						
Disruptive technology	Develop lentiviruses with higher payload and/or increase the efficiency of payload packaging using CRISPR and related site-specific integration					
						
Need	Developing cell lines that possess increased auto-resistance to their viral product					Productivity and failed lots, unit cost
Challenge	Increase virus and/or viral product production without loss of cell-line stability and with limited viral toxicity					
Potential solution	Increase resistance of cell lines to viral toxicity; 3D/suspension cultures that are not inhibited by high-virus titers					
						

Manufacturing Readiness Level

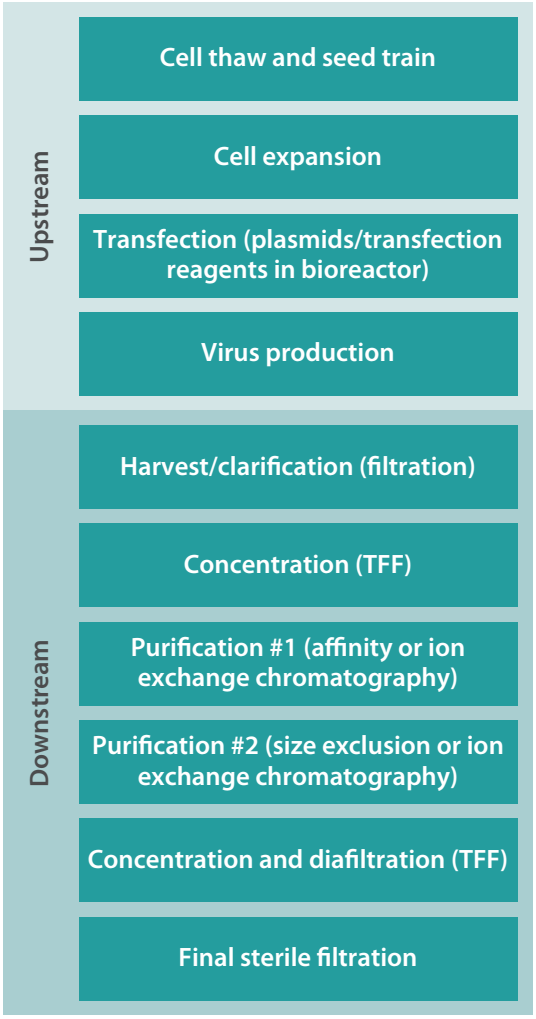
Research Development Manufacturing

3.2 Viral vector production process

Viral vector production processes are largely still in their infancy and would benefit from significant improvements in virtually all facets of their operation. This section summarizes the challenges and needs of many 'current state' production processes as well as some opportunities for improvement and the potential timings associated with each one.

While no 'standard' manufacturing process exists for the production of viral vectors, a general process flow might look something like that shown in Figure 3.

Figure 3: Typical production process flow for viral vectors



The upstream production process is normally divided into four major steps. Step 1 is the seed train where a vial from the master cell bank is thawed and the cells are transferred into a shake flask filled with a cell culture medium to initiate the cell growth. The cells are then transferred from the shake flask into a bioreactor to expand further. After the cell culture has reached the target cell density, the transfection mix containing the plasmids and the transfection reagent is added to the bioreactor. With the help of the transfection reagent, the plasmids penetrate the cells, which will then start producing the virus.

After several days of production, the virus is then harvested. Microfiltration using depth filters is typically used to remove solids (cells and/or cell debris), followed by a concentration step using TFF to reduce the volume. The concentrated virus is then purified using multiple chromatographic steps.

In the downstream operations, the first purification step may involve a chromatography-based capture step (e.g. affinity resin for AAV) capturing viral particles, while impurities such as host cell proteins and DNA are eliminated in the flow through. No such affinity resins exist for the purification of lentiviruses, so ion exchange chromatography is often used as the first purification step for these viral vectors. For both AAV and lentiviruses, trace impurities may then be removed using either size exclusion or ion exchange chromatography. Once purified, the virus is typically concentrated and stored in the required formulation buffer using TFF ultrafiltration and diafiltration before the final sterile filtration using 0.2 µm filters.

3.2.1 Upstream unit operations (cell thaw and expansion through transfection)

Since viral vectors are currently produced using animal cells, many of the same challenges faced by cell culture process technology, in general, apply to gene therapy vector production. Historically, a mammalian cell culture for recombinant proteins and viral-based vaccine production was limited first by cell type (since cultures were often anchorage-dependent cell lines) and then by the absolute concentration or 'density' of cells in the culture. By moving to suspension-capable cell lines, deep culture bioreactors could be used to both intensify and scale up manufacturing processes. These technologies, coupled with the development and optimization of nutrient media and modes of bioreactor operation, will further enable increases in cell concentration and therefore overall productivity.

See Tables 5 for a list of needs, challenges and potential solutions relating to upstream viral vector production.

Table 5: Viral vector production – upstream needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Optimize transient transfection to improve productivity					Productivity and failed lots, unit cost
Challenge	Reduce the number of plasmids required for transient transfection systems while not increasing chances of producing replication-competent viruses					
Potential solution	Develop a partially encoded cell line that does not produce replication-competent virus					
						
Disruptive technology	Stable producer cell lines that do not need transient transfection					
						

Manufacturing Readiness Level

 Research

 Development

 Manufacturing

Table 5: Viral vector production – upstream needs (continued)

		Current	3yrs	5yrs	10yrs	Impact
Need	Higher cell density to increase the volumetric productivity of viral particles					Productivity and failed lots, unit cost
Challenge	Limited cell density and process intensity with existing 2D technologies					
Potential solution	Move towards suspension cell lines (e.g. a HEK-293 cell line)					
		●	●	●	●	
Need	Optimize transient transfection step to reduce the amount of plasmid DNA and other costly reagents required, and increase virus productivity					Productivity and failed lots increase unit cost
Challenge	Complex set of interactions (e.g. DNA:cell, DNA:DNA, Reagent:DNA) that would need to be understood					
Potential solution	In-depth study using a 'design of experiment' approach to understand the interactions and optimize transfection conditions					
		●	●	●	●	
Need	Reduce the risk of contamination by adventitious agents in cell culture					Productivity and failed lots, unit cost
Challenge	Develop chemically defined media that are animal component-free and still support high cell concentrations without inhibiting virus production					
Potential solution	Develop animal-derived component media potentially using high throughput methods to screen media components for high cell growth and high virus production rates					
		●	●	●	●	

Manufacturing Readiness Level

● Research ● Development ● Manufacturing

3.2.2 Downstream unit operations (harvest through purification)

While the primary objective of a cell culture is to significantly increase the production of viral vector particles, the major downstream challenge is to develop a generic, scalable and reproducible purification process platform delivering high purity with high virus yield of recovery, while keeping intact the infectivity of viral vectors. The first challenge in downstream purification is the low yield of virus recovery. Each downstream unit operation leads to some loss of virus and/or virus activity and, therefore, a poor overall yield of recovery of infective particles throughout the entire purification process. A streamlined process with a reduced number of steps, limited pH and conductivity adjustments, and the use of filters with low virus adsorption and high volumetric throughput, will significantly increase the recovery of intact viral vectors. Another important limitation of existing purification processes is the ability to achieve a high virus purity. Highly resolutive separation techniques are necessary to isolate the fully potent viral vectors from cellular- (host cell proteins and DNA) and product-related (empty and partially filled capsids) impurities.

Many early downstream processes relied on purification techniques that were challenging to scale up (e.g. CsCl gradient ultracentrifugation) or not commercially available at larger scales (e.g. small-batch produced chromatography resins that are not well validated and documented for compliance with cGMP). These processes are hence not optimal for manufacturing at scale. Scalable and commercially available purification techniques from process development to commercial manufacturing is therefore required.

Finally, the development of generic process platforms, where the techniques used will be suitable for the purification of multiple virus vectors and serotypes will address the need for process comparability and regulatory compliance. Prior knowledge of the development of process platforms for the purification of monoclonal antibodies should shorten the time to develop such generic platforms for gene therapy and consequently accelerate the accessibility to patients.

See Tables 6 for a list of needs, challenges and potential solutions relating to downstream viral vector production.

Table 6: Viral vector production – downstream needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Reduce loss of viral particles during primary recovery and clarification					Productivity and failed lots, unit cost
Challenge	Develop efficient harvest and clarification steps while maintaining viral vector potency					
Potential solution	Use of low adsorption and high throughput primary recovery and clarification techniques					
		●	●	●	●	
Need	Reduce loss of viral particles during downstream virus purification steps					Productivity and failed lots, unit cost
Challenge	Typical chromatography techniques for the purification of viral vectors make use of harsh conditions (e.g. pH and conductivity) that lead to viral inactivation					
Potential solution	Develop and introduce a streamlined purification process that employs process conditions that do not disrupt viral vector structure and function					
		●	●	●	●	
Need	Increase the purity of viral vector product pools					Product safety
Challenge	Achieving sufficient clearance of process- and product-related impurities while maintaining high product recovery					
Potential solution	Develop highly selective techniques for removal of residual impurities					
		●	●	●	●	
Need	Develop a scalable purification process					Cost and flexibility
Challenge	Some purification strategies that enable high viral vector purity are not scalable (e.g. CsCl gradient ultracentrifugation)					
Potential solution	Development of highly selective and scalable separation techniques from process development to commercial manufacturing					
		●	●	●	●	
Need	Reduction of lot-to-lot variability of viral vectors produced and purified from manufacturing processes					Productivity and failed lots, unit cost
Challenge	Inherent lot-to-lot variability of multiple manufacturing processes used for the same or similar viral vectors					
Potential solution	Establish process platforms suitable for multiple viral vectors and serotypes					
		●	●	●	●	

Manufacturing Readiness Level

● Research ● Development ● Manufacturing

3.2.3 Formulation/stability and fill/finish

Similar to the development of gene therapy vector-specific upstream and downstream unit operations, the extension of the relatively well developed field of protein formulation science to viral vectors is still in its infancy. Some progress was accomplished in the earlier phase of gene therapy evaluation in the late 1990s regarding the development of more robust formulations for viral vectors, specifically for the hardier classes of non-enveloped viruses such as adenoviruses and AAVs. However, progress in formulation development for enveloped viruses (such as lentiviruses, herpes viruses and other retroviruses) has lagged significantly, most likely due to the sensitivity of this family of viruses to changes in pH and temperature.

Regarding formulation development for enveloped viruses, some viruses exhibit a threshold, which abruptly impacts on the virion structure above a specific temperature. Therefore, temperature studies need careful consideration in terms of investigating this threshold effect or the impact of cumulative excursions near a threshold. Lyophilization has been investigated as a means of ensuring stability under long-term storage conditions. However, current limitations exist in the ability to accurately and precisely detect virus potency. Expanding the list of critical quality attributes (CQAs) beyond infectivity would be helpful in determining the routes of viral vector degradation in different buffers and under different extrinsic conditions to achieve formulation improvements.

The temperatures required for storage and shipment of viral vectors could be -40°C or -70°C (or below). The latter conditions could lead to a complicated cold supply chain. Although not a manufacturing consideration, the need for cold shipments of viral vector samples (-70°C or below) often requires shipment on dry ice. For shipment of bulk material, drug product or samples on dry ice, the considerations around containers with a low permeability to carbon dioxide vapor are even more important to heed for viruses than proteins, due to the typical instability of viruses at low pH.

From a filling perspective, shear effects during dispensing need to be carefully considered and mitigated. Open filling from a needle represents a break in the closed system handling of what are often BSL-2 viruses. This can create greater demands regarding facility containment capabilities than for protein fills. One last area of concern is the type of drug product vial itself. For some vectors, moving away from glass to polymeric vials decreases potential safety issues by ensuring safe containment of the vector.

See Tables 7 for a list of needs, challenges and potential solutions relating to formulation/stability and fill/finish.

Table 7: Formulation/stability and fill/finish – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Improved viral vector formulations with extended stability at low and high temperatures					Productivity and failed lots, unit cost
Challenge	*Ex vivo* viruses are highly labile					
Potential solution	Improved formulations (e.g. excipients) to increase shelf-life stability at any storage condition					
		●	●	●	●	
Need	Elimination of shear stress due to needle-based filing operations					Productivity and failed lots, unit cost
Challenge	Achieve precise filling requirements in a non-needle-based system					
Potential solution	Precise low-shear filling operation					
		●	●	●	●	
Need	Strict aseptic drug product filling lines to avoid additional sterile filtration					Productivity and failed lots, unit cost
Challenge	Repetitive sterile filtrations are unreasonable given product losses					
Potential solution	Real-time sterility testing; closed end-to-end processes					
		●	●	●	●	

Manufacturing Readiness Level

● Research ● Development ● Manufacturing

3.2.4 Viral analytics

Analytics for in-process testing, product characterization, lot release and stability testing are essential for supporting the clinical development of biological therapeutics and, ultimately, product commercialization. Specific to gene therapies, measuring the attributes of DNA or RNA as a drug substance or drug product is relatively straightforward and mainly involves the evaluation of sequence fidelity, well described biochemical modifications and their potential structure. However, the efficacy, potency and toxicity of many gene therapies are largely driven by the emulsion (e.g. liposomes or biopolymer complexes), particle (e.g. lipid nanoparticles), viral vector or mechanical device (e.g. electroporator) that deliver the gene(s).

Most of these gene delivery modalities are inherently complex and, considering the industry's lack of experience in commercializing gene therapies, then chemistry, manufacturing and controls will face many challenges for developing and implementing the required analytics for rigorous product characterization and quality assessment. This section focuses solely on the analytical challenges and needs for gene therapies delivered by viral vectors; however, much of this section also relates to gene therapies delivered by other modalities.

Viral vector titration, % vector filled, genome copy number, vector size and composition, and potency are just a few attributes of viral vector-based gene therapies that are challenging to measure with reliable accuracy, precision and reproducibility. For example, current methods that measure viral vector size distribution, such as transmission electron microscopy and analytical ultracentrifugation, are laborious and not easily adaptable to cGMP environments. Similarly, current methods that measure viral vector titration (including qPCR, ELISA and focus-forming assays) are not platformed across the industry and are notoriously variable.

'Mechanism of action'-reflective potency assays also pose a large hurdle for gene therapies. The mechanism of action of all gene therapies is multifaceted and includes transfection/infection, gene transcription and/or translation, and action of the translated protein. Thus, there are many possible stages of the mechanism of action to capture within a single potency assay. Moreover, the current lack of in vitro to *in vivo* translation for biological assays challenge whether in vitro measurements of potency, efficacy, cytotoxicity and/or immunogenicity are physiologically meaningful and predictive.

A common challenge to the manufacture of gene therapies is the cost of analytics. Current manufacturing and purification processes result in relatively low product yields. Thus, the battery of analytics required for complete in-process testing, product characterization, lot-release and stability testing can consume significant amounts of clinical lots. Also, and as with most biological therapeutics, reference standards for a given gene therapy are generated from designated clinical lots. Thus, the poor yield and high variability of manufacturing gene therapies, combined with the required amount of analytical testing, can result in the frequent generation of new clinical lots and reference standards.

Moreover, current practices for qualifying reference standards are not harmonized across the industry and rely on laborious and variable analytics.

Innovative technologies and methodologies (with potential application for in-line, real-time and/or non-destructive analytical testing in cGMP environments) will help to overcome many analytical challenges for manufacturing and developing gene therapies. The use of 'design of experiment' and 'quality by design' approaches when developing these novel technologies, or when implementing current technologies, will ensure gene therapy analytics are robust and meet the acceptable levels of assay performance for confident product characterization and quality assessment.

Also, combining innovative technologies with harmonized procedures for qualifying reference standards will increase the validity of analytical testing and confidence in results.

See Tables 8 for a list of needs, challenges and potential solutions relating to virus analytics.

Table 8: Virus analytics – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Robust and standardized analytical testing strategy for viral vector-based products					Product quality and consistency, production costs
Challenge	Current analytical testing strategy varies across the industry. Also, current analytics lack the precision, accuracy and reproducibility required for confident dose-determination, lot-to-lot comparison, cGMP testing and product characterization					
Potential solution	Adopt innovative analytical techniques that demonstrate high accuracy, precision and reproducibility; optimize and harmonize assay preparation procedures, materials and readouts across the industry; implement 'design of experiment' and 'quality by design' to develop robust assays					
		●	●	◐	●	
Disruptive technology	Technologies with potential for in-line and/or in real-time analytical testing; non-destructive analytical methods; innovative chromatography stationary phases and orthogonal high-resolution separation techniques; novel virus-counting technologies and viral-titration assays; and more physiologically relevant in vitro systems for potency measurements and biological characterization					
		●	●	◐	●	

Manufacturing Readiness Level

● Research ● Development ● Manufacturing

Table 8: Virus analytics – needs (continued)

		Current	3yrs	5yrs	10yrs	Impact
Need	Standardized qualification package for harmonizing the production of standards					Product quality
Challenge	Current strategies and methodologies vary for preparing and characterizing reference standards					
Potential solution	Develop robust and harmonized procedures for qualifying reference standards					
		●	●	●	●	
Need	Identification and characterization of CQAs and process- and product-related impurities					Product quality and consistency, production costs
Challenge	Lack of knowledge of viral vector structure-function relationships from a therapeutic standpoint. Also, limited experience and variation of manufacturing and purification processes hinder identification of common process- and product-related impurities					
Potential solution	Develop a standardized template for a quality target product profile; application of novel technologies and methodologies for impurity identification, forced-degradation and structure-function investigations; more translatable in vitro biological assays to better assess physiological relevance of CQAs and impurity impact on potency, efficacy and toxicity					
		●	●	●	●	

Manufacturing Readiness Level

● Research ● Development ● Manufacturing

3.3 Viral vector production - facilities needs

Gene therapy facilities typically fall under two operational modalities, ones producing viral vector intermediates and those producing drug substance and product. In certain instances, there is a need for one facility to support all modalities while in other, the facility need may be singular. Due to the nature of these processes, and the facility needs required to support viral production, existing infrastructure is not suitable for gene therapy production without an expensive site retrofit. As such, facilities are often purpose-built for gene therapy applications.

Demand for manufacturing space for viral vector production is outpacing capacity. As a result, there is a large backlog in capacity at many contract development and manufacturing operations for companies that do not have in-house manufacturing. This trend is anticipated to continue for at least the next five years.

These facilities need multiple, small, processing spaces with proper segregation. As a result, they need to be modular, mobile and autonomous. Cleanrooms must support segregated BSL-2 spaces and should allow for incremental additions of capacity on site.

Larger ballroom designs are not suitable as they have overly cumbersome procedure-based quality systems and there is the risk of cross-contamination, resulting in multiple batch losses.

The solutions and impacts in this area have been well defined in the BioPhorum Biomanufacturing Technology Roadmap: Modular and Mobile [7]. The solutions defined in this BioPhorum roadmap describe how standardization, coupled with modular and mobile design, can help drive down costs while also addressing other major drivers such as speed to market and flexibility. Differentiated cleanrooms that could support hazardous environments (e.g. ATEX or Class 1 Division 1/2) may be needed in the future. As such, the mobile aspect of cleanrooms is critical to support change-out needed for technology migration.

3.4 Regulatory science and standards needs

To improve the consistency and quality of the virus vectors used in gene therapy applications, the manufacturing industry must work with regulatory agencies (including the FDA, the European Medicines Agency (EMA) and other global regulators). Together these organizations can work to define the standards needed for virus vector manufacturing process and product testing, and to help develop regulatory guidance for viral vector-based gene therapy products and processes. Establishing standard materials and testing procedures for manufacturing processes, testing and releasing is critical to drive the development of innovative gene therapy products and efficiently move them to commercialization and clinical use.

To realize large-scale, cost-effective and reproducible manufacturing of virus vectors to support gene therapy, the manufacturing community must address the following standardization and regulatory challenges.

Difficulty defining the products of biological processes: virus vectors used in gene therapy are manufactured primarily from eukaryotic cell substrates. As viruses are complex biological molecules, the specific processes used in manufacturing will be as important as the analytics involved in characterization and testing. The actual molecular composition of the virus vectors will be impacted by the cell substrate, the metabolic state of that substrate during production and the media used for production. Because of this complexity, it is recommended specific reference standards for the most common gene therapy virus vectors are developed. This would include AAV strains of interest [8], adenovirus, lentivirus and gamma-retrovirus. As an example of this effort, the National Institute of Standards and Technology has produced an adenovirus 5 reference standard is now available from the ATCC.

Lack of product consistency across the supply chain: due to concerns about product consistency across the supply chain, many 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.

Regulatory strategy development: the gene therapy industry must coordinate with global regulatory and related agencies (including the FDA, the Centers for Medicare and Medicaid Services, the EMA and the International Conference on Harmonization) to formulate a strategy for developing and harmonizing gene therapy regulations. This strategy will also inform the development of personalized gene therapy applications, such as personalized viral vectors for treatment. Keeping these agencies informed about emerging technologies and techniques will help the gene therapy community advocate for regulations that can continuously drive industry advances. cGMP guidance for Advanced Therapy Medicinal Products is available on the EMA website [9]. Useful guidance related to gene therapy is available at the FDA website [10]. Also, there some FDA pathways toward an expedited review of cell and gene therapy [11, 12].

Product quality standards: improved product consistency could allow the virus vector manufacturing community to more accurately predict patient responses to gene therapy products. Increasing standardization of assays and inspection methods for product release and developing reference standards for various cell types, could help improve the 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 gene therapy products.

3.5 Workforce development and needs

Like most innovation-focused industries, biopharmaceutical industry growth depends on an educated, highly skilled, flexible and high-performing workforce. As gene therapy emerges as a promising and likely transformative new therapeutic direction for many patients, it will undoubtedly present new challenges concerning workforce preparation and development. The challenges noted below are potentially far-reaching across all segments of the workforce, including scientists, engineers, technicians and senior management.

Industry challenges: there is a significant need for cross-disciplinary training in the industry to support gene therapy manufacturing processes. While protein-based therapeutics benefit from platform scale-up and production processes, and years of best practice sharing, gene therapy presents a unique challenge in that both the products and processes are new.

Compared to the more familiar handoff from development to manufacturing for traditional biopharmaceuticals, technology transfer for gene therapy processes from development to manufacturing will likely involve far greater collaboration between R&D and process-focused teams. Process-focused scientists and engineers must understand the nuances and complexities involved in processing viral vectors to successfully transfer processes from development labs into commercial manufacturing.

Similarly, there will be a growing need for bench scientists that understand industrial processing. Industry-based and academic researchers are very familiar with producing research and early clinical quantities of AAV and other vectors. However, these bench scientists must also understand industry-scale unit operations, commercialization, technology transfer and scale-up. There are several foundational skill gaps, including an applied understanding of:

- cGMP
- product-commercialization pathways
- manufacturing-scale unit operations
- process and industrial virology
- most critically, scale-up considerations unique to gene therapy.

Filling these knowledge and skill gaps will enable researchers to select scalable unit operations, reduce bottlenecks and conduct early product and process development work that transfers smoothly into clinical and commercial manufacturing.

Academic challenges: in addition to educating the next generation of biopharmaceutical industry professionals, specialized academic centers of excellence already add value by providing instruction, hands-on training and contract services. Many of these centers already have strong knowledge of cGMP and manufacturing-scale unit operations, but the manufacture of gene therapies presents new challenges. For example, academic partners must understand gene therapy manufacturing best practices, biosafety facility requirements, analytical methods, product quality attributes and other challenges unique to gene therapy to add even greater value in this emerging area.

Enhanced collaboration and communication challenges: gene therapy is still in its infancy. As a result, there are still many unanswered questions concerning knowledge, skill and workforce development needs. For this reason, ongoing collaboration and communication between gene therapy industry pioneers, subject matter experts and educators is critical to ensure tomorrow's workforce is prepared.

4.0 Conclusions and recommendations

This Gene Therapy Roadmap has been prepared by a cross-section of stakeholders (including those from academia, manufacturers, suppliers and government) resulting in what the team believes to be balanced and comprehensive content. This roadmap is intended to serve as a 'living document' representing aspects of the current state-of-the-art in viral vector-based gene therapy.

The key conclusions and recommendations from this roadmap are:

1. **starting materials:** consistent, large-scale plasmid production and purification are central to the development of the genetic material required for gene therapy. Current plasmid production processes are limited in terms of production capability. Enhanced capability is required for improved supply chains for gene therapy
2. **upstream processing:** many current viral vector processes still employ adherent cell culture systems. Significant optimization, including use of suspension-based cultures, is needed to improve overall batch productivity and consistency
3. **formulation/stability and fill/finish:** many ex vivo viruses are inherently unstable for a number of reasons and work should be done to improve their robustness, preferably through optimized formulation
4. **analytics:** many of the contemporary analytical methods used to evaluate product yield, potency and purity lack the specificity and precision needed to ensure robust batch-to-batch product quality. New in-line and off-line technologies should be developed and integrated into gene therapy processing
5. **facilities:** due to the unique nature of viral vector processing (in particular, scale and safety considerations), solutions will be needed to allow for the flexibility and aseptic capabilities required for multiple products
6. **regulatory sciences:** early engagement with global regulators is needed to improve product consistency and quality, and help to ensure the smooth passage from early stage (Investigational New Drug) to commercial stage (Biologics License Applications) operations
7. **workforce:** there is a significant need for cross-disciplinary training to support gene therapy technology transfer and manufacturing operations. Ongoing collaboration and communication between gene therapy pioneers, subject matter experts and educators are critical to ensure tomorrow's workforce is prepared.

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Acronyms/abbreviations

AAV	Adeno-associated virus
cGMP	Current good manufacturing practices
CQAs	Critical quality attributes
DNA	Deoxyribose nucleic acid
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GOI	Gene of interest
NIIMBL	National Institute for Innovation in Manufacturing Biopharmaceuticals
RNA	Ribose nucleic acid
TFF	Tangential flow filtration

Collaboration Statement

This document is the result of a collaboration between the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and BioPhorum Operations Group (BioPhorum) to develop a NIIMBL roadmap for the biopharmaceutical manufacturing industry, which complements the existing Biomanufacturing technology roadmap and other industry roadmaps.

https://www.biophorum.com/executive-summary/

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Our hope is that it presents areas of opportunity for potential solutions facing the industry and encourages innovation and research and development for the biopharmaceutical industry community to continue to evolve successfully to serve our future patient populations.

Disclaimer

Roadmap team members were lead contributors to the content of this document, writing sections, editing and liaising with colleagues to ensure that the messages it contains are representative of current thinking across the biopharmaceutical industry. This document represents a consensus view, and as such it does not fully represent the internal policies of the contributing companies. Neither NIIMBL nor any of the contributing companies accept any liability to any person arising from their use of this document.