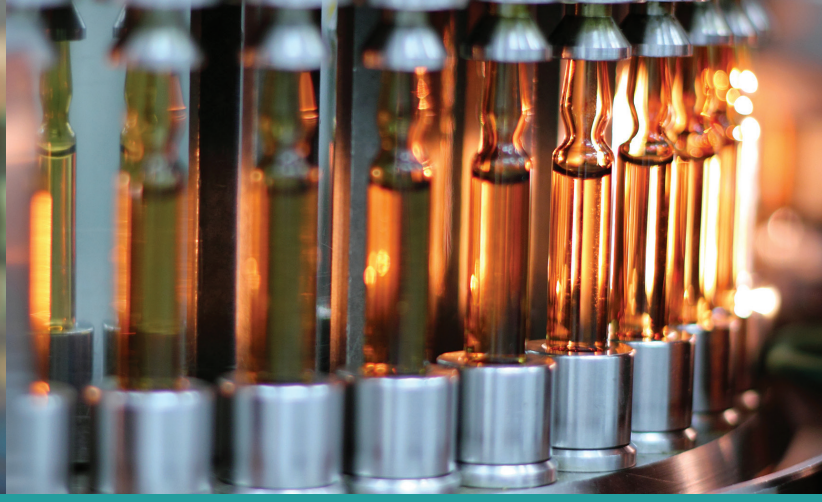

NIMBL

The National Institute for Innovation in Manufacturing Biopharmaceuticals

Vaccines 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 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.

This NIIMBL Vaccines Roadmap provides a vision of the future of vaccines and addresses the market trends and business drivers influencing the discovery, development and manufacturing best practices for these biotherapeutics worldwide. It then discusses the future needs and challenges associated with the manufacturing of vaccines and proposes some potential solutions to these production barriers. There are numerous issues that are covered, including process development, supply chain, rapid analytical methods, modeling, knowledge management and regulatory science and standards development.

Most of these issues span the entire production process including upstream and downstream processing, and final drug product (DP) 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.

This Vaccines Roadmap intends to demonstrate how meaningful benefit over current practices may be achieved by systematically addressing the identified biomanufacturing needs. Addressing these needs will improve affordability and accessibility through a robust and reliable supply of vaccines. This is essential to protect broader populations and future generations from preventable and treatable diseases.

Benefits to biopharmaceutical manufacturing can be obtained by implementing the various potential solutions and disruptive technologies mentioned in this document over the long term. The key conclusions and recommendations from this roadmap are:

1. **investment:** continued investment in vaccine innovation (e.g. pipelines to address new infectious diseases; robust, reliable supply with a low cost of goods (CoGs); enabling safe, effective and quality products) to address the global aging population and birth cohorts
2. **regulation:** simple and clear regulatory pathways, especially for enabling innovative approaches for vaccine process, analytics and formulation solutions
3. **open innovation:** a sustained collaboration among industry, suppliers, regulators and research communities.

2.0 Introduction

Vaccines are generally considered to be one of the most cost-effective health interventions to fight infectious diseases, as illustrated by the global eradication of smallpox, the near-eradication of polio and the reduced burden of diphtheria, tetanus, measles, mumps, rubella, etc. Vaccines save millions of lives each year while lessening the financial burden on healthcare budgets. The Center for Disease Control estimates more than two billion children have been vaccinated since 2001 and the measles vaccination alone has saved more than 20 million lives between 2000 and 2015. In addition to the direct impact on human healthcare, vaccines for domestic and livestock animal populations serve to maintain animal welfare and act as an important barrier to the transmission of zoonotic diseases. This latter point may be critical to the prevention and control of future pandemics since, according to the Center for Disease Control, scientists estimate three out of four new or emerging infectious diseases are zoonotic by nature [1].

It should be noted that preventative vaccines are administered to healthy populations and often rely on large clinical study designs due to a lack of accurate and reliable data reflecting the immune correlate of protection for treatment effectiveness. Furthermore, with the advent of personalized medicine, therapeutic vaccines provide an alternative pathway for reducing disease burdens globally. Despite the benefits of and continued investments in vaccines for new and emerging infectious diseases (e.g. Zika, Ebola), the globalization of vaccines remains a challenging task.

The affordability and accessibility of vaccines remains a challenge and is further complicated by:

1. multiple modalities (e.g. proteins, polysaccharides, conjugates, live attenuated viruses, killed whole viruses or bacteria) often using complex batch processes for drug substance (DS) and DP production
2. composition complexity and the lack of well-defined structure/function correlations leading to challenging analytics (e.g. infectivity assays)
3. the intrinsic instability of vaccines often coupled with the lack of an established cold-chain footprint in several politically and economically sensitive geographical areas
4. multiple local regulatory agencies providing different guidance and additional release steps
5. industry growth and innovation requiring the parallel growth of a well-trained vaccines-job-related workforce, academic curriculum and vaccine awareness.

2.1 Vision

This document aims to demonstrate how global access to affordable vaccines can be enabled by developing safe and effective, high quality products that address high-priority vaccine biomanufacturing needs. The authors acknowledge developments are required to enable creation of new modalities, thermostable products and patient-centric products. Knowledge building and a skilled workforce are recognized as critical enablers to create reliable, robust, low-cost manufacturing processes and expedited licensure. Collaboratively addressing these sector needs is the most efficient way to ensure the world's population can benefit from improved health outcomes.

2.2 Market trends and business drivers

The market trends affecting the biopharmaceutical industry have been comprehensively described by other roadmaps, including BioPhorum's Biomanufacturing Technology Roadmap [2], and can generally be summarized in terms of four major trends. These are the continued growth of the biopharmaceutical market, increasing numbers of new product classes including vaccines, rising cost pressures and the uncertainty of product approvals and sales.

Other important trends (such as the development of flexible facilities, continuous processing and knowledge management) are applicable across the spectrum of biopharmaceutical modalities. However, the field of vaccines is also challenged by these specific market trends:

1. the complexity and diversity of vaccines coupled with the lack of well defined structural/functional correlations, result in clinical pathways that are complex to commercailize. Thus, the need for novel vaccine products, smart clinical trials and biomarker improvements are essential to reaping the complete benefits of vaccines
2. current vaccines often need a cold-chain throughout their lifecycle due to their intrinsic instability compared to small molecule and/or biologic drugs. Thus, the need to improve their affordability and accessibility often goes above and beyond the trends identified in the Biophorum's Biomanufacturing Technology Roadmap [2]
3. vaccines, especially in the case of an outbreak, may require rapid end-to-end development and production while maintaining safety, quality and efficacy of the product
4. the need to improve vaccination rates and compliance with vaccination recommendations may require the development of alternate delivery routes and/or combination products.

Each potential solution and disruptive technology discussed in Section 3 below, was considered in the context of the likely impact on vaccine business drivers.

The technology focus areas and priorities should enable advancement of at least one core vaccine business driver, a few of which are:

1. improved patient adherence and reduced immunization burden, with patient-friendly storage and delivery systems (e.g. combination vaccines and newer modalities, understanding of molecular attributes to their clinical relevance, thermostable products, mucosal or needle-free delivery)
2. reliable and robust supply chain (e.g. no shortage of supply, reduce inventory through on-demand manufacturing, wastage reduction by improving the shelf-life of vaccines)
3. automated fit-for-purpose facilities for improved agility and efficiency (e.g. modular, mobile, plug-and-play, scale-out versus scale-up, localized manufacturing, reconfigurable multi-product facility)
4. predictive and prescriptive analytics to enable real-time release (RTR) and continuous manufacturing
5. knowledge management across process and product development, manufacturing, technology transfer and regulatory filings.

We believe pronounced benefits can be obtained by implementing the various potential solutions disruptive technologies and approaches mentioned in this document over the long term, but this will require a sustained collaboration among industry, suppliers, regulators and research communities.

2.3 Scope and links to other roadmaps

This roadmap assesses the current state of manufacture as well as the future technology and capability needs relating specifically to vaccines and covers these topic areas:

- production facilities
- DS process development
- DP process development
- analytical
- modeling
- knowledge management
- workforce development
- regulatory and science standards.

Technology considerations relating to general monoclonal antibody manufacture are described by BioPhorum's Biomanufacturing Technology Roadmap [2] and are therefore not included in this document.

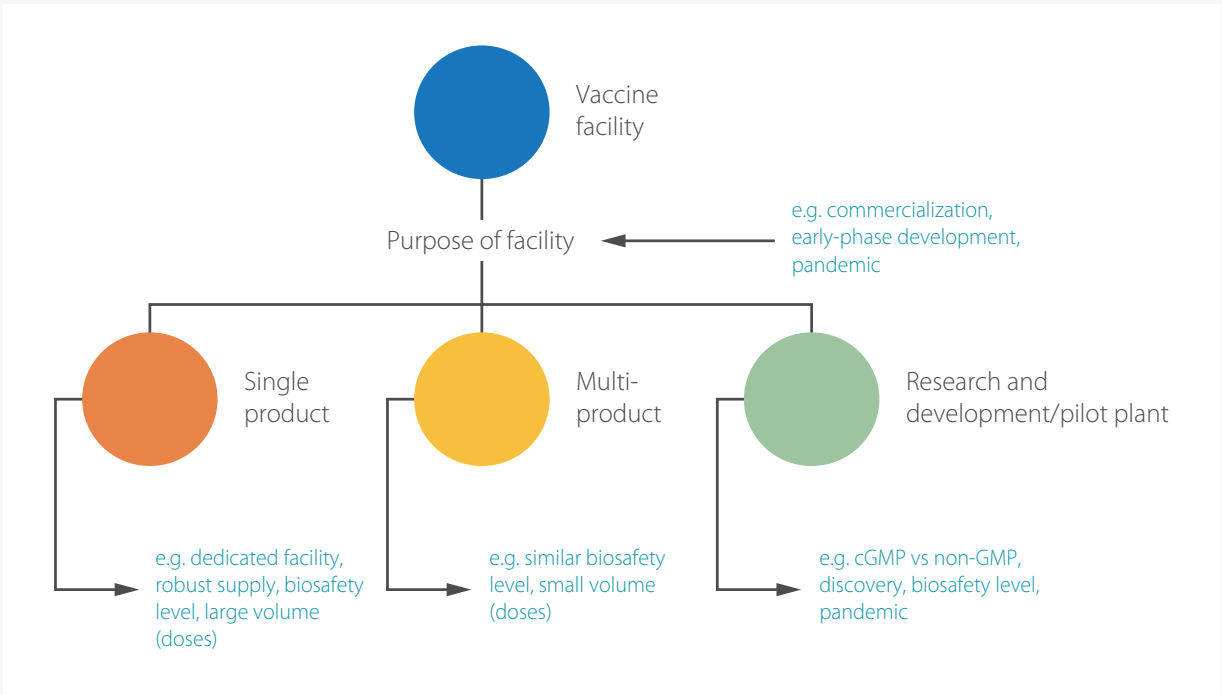
Technology considerations relating to general lyophilization in the manufacturing process are described by the LyoHub Roadmap [3] and are therefore not included in this document.

3.0 Future needs, challenges and potential solutions

3.1 Production facilities

Given the complexity and diversity of vaccine manufacturing processes and supply chains, there is a need to be conscious of those aspects that drive the different facility types and appropriate, fit-for-purpose solutions. Figure 1 shows how key considerations vary according to the purpose of the facility.

Figure 1: Facility tree demonstrating considerations associated with single-product manufacturing plant, multi-product manufacturing plant and an R&D/pilot-plant facility



Aspects such as process compatibility, a robust supply to meet market demand, biosafety level (BSL), single vs. multi-product facilities and the scale of manufacturing are some of the drivers that define facility designs.

Vaccine manufacturers should, however, aim to make facilities more agile, flexible and repurposable for future products, which can extend the facility lifecycle and can allow for capacity additions without interrupting current operations.

It is the aspiration of the authors that all types of facilities, as a minimum, need to provide adequate:

- flexible, current good manufacturing practice space
- standardized utility connections
- open-architecture automation systems.

These could, in turn, accommodate the rapid installation of plug-and-play unit operations for DS manufacture through to packaging and release.

For the above aspiration to be realized, there need to be advances in single-use (SU) technologies in the areas of larger commercial-scale bioreactors (i.e. 2,000–5,000L+), chromatography and centrifugation, solvent handling, bioburden control and the closed processing of all unit operations. These will enable a modular, plug-and-play approach to vaccine manufacturing while minimizing production costs.

Future vaccine manufacturing plants should be constructed of modular units that enable multiple configurations. Modular design, however, can be established at various levels, e.g. site, building, room, unit operations.

We propose biopharmaceutical companies, regulators, vendors and contractors catering to the sector collaborate to set requirements around the fabrication, installation and qualification of these facilities and technologies and therefore streamline the path to licensure. Advances in these areas are critical to expanding global access to vaccines by reducing supply chain complexity (i.e. cold-chain storage/transport) as well as addressing country-specific manufacturing requirements. Also, the application of modular and standardized facilities with a streamlined path to licensure would greatly enhance the ability of the vaccine industry, in partnership with global health organizations, to quickly respond to disease outbreaks while maintaining adequate supply and product quality.

See Table 1 for a list of production facility needs, challenges and potential solutions.

Table 1: Production facilities – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Multi-product facilities with plug-and-play capabilities for various unit operations					Affordability, speed to market, supply chain robustness, streamlined validation, speed to configure and scale
Challenge	Diversity of vaccine unit operations; scale and BSL differences across portfolios; product segregation; high capital investments					
Potential solution	Designed, current good manufacturing practice flexible spaces with universal utility connections and open-architecture automation					
		●	●	●	●	
Need	Multi-configuration facilities that enable rapid, end-to-end vaccine manufacture					Affordability, speed to market, supply chain robustness, improved market accessibility
Challenge	Diversity of vaccine unit operations does not readily enable standardization of modular designs; scale and BSL differences across portfolios; product segregation					
Potential solution	Collaboration of industry, regulators and vendors to establish facility requirements and streamline the path from concept and fabrication to licensure					
		●	●	●	●	
Disruptive technology	Self-contained facilities; streamlined validation; streamlined approval process for high-BSL products or pandemic products					
		●	●	●	●	
Need	Larger commercial-scale SU bioreactors (e.g. 2,000–5,000L+)					Affordability, supply chain robustness
Challenge	Gas-transfer and mixing limitations; SU bag design; container integrity; handling and ergonomics					
Potential solution	Alternate agitation assembly, sparger and bag designs; robotics/automation					
		●	●	●	●	
Disruptive technology	Commercial-scale SU fermenter to support microbial-based processes; BSL (level 2) SU reactor systems					
		●	●	●	●	

Manufacturing Readiness Level

Research	Development	Manufacturing
●	●	●

Table 1: Production facilities – needs (continued)

		Current	3yrs	5yrs	10yrs	Impact
Need	Cost-effective SU technologies (e.g. chromatography, centrifugation)					Agility, affordability, speed to market, supply chain robustness
Challenge	Due to variable production scales, materials can be low-volume and high-cost; high pressure and other process constraints are incompatible with SU technologies					
Potential solution	Vendor and technical collaborations					
		●	●	●	●	
Need	Innovative engineering solutions for solvent-handling capabilities					Affordability, speed to market, supply chain robustness, flexible on-demand manufacturing, streamlined validation
Challenge	Current explosion-proof engineering solutions are fixed and costly with long lead times					
Potential solution	Safe, environmental monitoring-friendly, solvent-compatible hybrid facilities with a mix of stick-built and modular transportable units					
		●	●	●	●	
Need	Robust technologies for facility bioburden control					Affordability, speed to market, supply chain robustness
Challenge	Historical facility controls have occasionally been insufficient for bioburden control (e.g. control of source material)					
Potential solution	SU equipment, novel equipment, component or engineering solutions					
		●	●	●	●	

Manufacturing Readiness Level

● Research ● Development ● Manufacturing

3.2 Drug substance process development

Vaccine process development uses a wide variety of biological systems, including native and/or recombinant-based expression systems, using prokaryotic, eukaryotic, and/or virus production methodologies.

Traditional and novel vaccine production technologies include:

- fermentation and cell culture: e.g. cell stacks, roller bottles, microcarriers, batch/fed-batch/perfusion, stirred-tank bioreactors
- mid-stream recovery: e.g. inactivation, cell lysis, homogenization, flocculation, filtration, centrifugation and refolding
- downstream purification: e.g. precipitation, depth filtration, tangential flow filtration, phase extraction and chromatography.

In many cases, antigen purification is followed by an additional inactivation step and/or chemical conjugation with a carrier protein that requires additional purification unit operations.

Furthermore, the vaccine development cycle practice of having an early 'process-lock' during clinical trials often leads to lower process productivity relative to demand. Thus, in the future, the complexity of vaccine baseline technologies must be considered when meeting the industry's challenge for global supplies manufactured in right-sized, flexible, multi-product facilities.

To enable robust, low-cost vaccine manufacturing with the goal of improved global access and affordability, several advances in DS process development are needed as follows.

For fermentation and cell cultures, challenges include the development of new cell lines and antigen expression systems. These include cell-free methods; efficient cell-expansion unit operations for both adherent and suspension cell lines; chemically defined, animal component-free (ACF) base media for both eukaryotic and prokaryotic cell lines; and an increased understanding and modeling of the relationship between cellular growth kinetics, metabolism and product expression (discussed in Section 3.5).

For mid-stream recovery and downstream purification, challenges include the development, design and implementation of right-sized harvest/clarification platforms that are capable of realizing upstream productivity gains and allowing for truly multi-product facilities with a thoughtful combination of fixed stainless steel and disposables manufacturing technologies. To achieve this goal, the development of novel impurity targeting and removal approaches (e.g. new flocculants, cell-free production systems) may provide the advantages of efficient, robust clarification technologies. Also, the development and implementation of antigen-specific affinity purification media delivering better selectivity directly from complex feed solutions is also required to facilitate the clearance of both process- and product-related impurities. Effort in developing platform chemistries for more efficient and site-directed activation and conjugation of DSs (i.e. capsular polysaccharide, small molecule and carrier protein structures) is needed as well as novel sterile filtration technologies capable of handling the resulting large vaccine modalities without impacting product yield or quality.

Across all DS manufacturing unit operations, there is also a need to advance the application of continuous manufacturing principles to reduce cost and improve supply robustness, especially for large-market, high-labor, vaccine products (i.e. some live viral vaccines). There is also a need to develop advanced process monitoring and analytical tools to better understand critical product quality attributes, safety and efficacy sooner in the development cycle (discussed in Section 3.4).

Advances in each of the areas above will improve speed to market and enable the goal of developing well characterized cost-effective vaccines.

See Table 2 for a list of drug substance process development needs, challenges and potential solutions.

Table 2: Drug substance process development – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	High-productivity expression systems					Affordability
Challenge	Product diversity and tropism do not enable the development of 'universal' expression systems, cytotoxic or lytic products, adventitious agent risks					
Potential solution	Novel cell lines; synthetic promoters and transcription factors; enhanced post-translational modification and protein folding machinery					
		●	●	●	●	
Disruptive technology	Cell-free expression systems, e.g. mRNA					
		●	●	●	●	

Manufacturing Readiness Level

●	●	●
Research	Development	Manufacturing

Table 2: Drug substance process development – needs (continued)

		Current	3yrs	5yrs	10yrs	Impact
Need	Low-cost, efficient cell-expansion technologies					Affordability, supply chain robustness
Challenge	Cell expansion is often rate-limiting for DS manufacture, especially for anchorage-dependent cell lines					
Potential solution	High-density cell banks					
		🟡	🟡	🟢	🟢	
Disruptive technology	High-density, low-footprint cell expansion technologies (e.g. fixed-bed bioreactors, degradable microcarriers) and/or direct-to-production high-density cell banks					
		🔴	🟡	🟡	🟢	
Need	Chemically defined-ACF (CD-ACF) base media					Affordability, speed to market, supply chain robustness
Challenge	Use of CD-ACF medium typically results in reduced productivity and/or increased cost/ volume. Not all cell lines are adaptable to CD-ACF medium					
Potential solution	High-throughput screening models and databases for representative cell lines					
		🔴	🔴	🟡	🟢	
Disruptive technology	'Universal' base, chemically defined-ACF media for both eukaryotic and prokaryotic cell lines					
		🔴	🔴	🔴	🟡	
Need	Novel methods of removing/targeting impurities, e.g. flocculants					Affordability, speed to market, supply chain robustness
Challenge	Selective precipitation/removal of host cell/process impurities for a wide variety of expression systems					
Potential solution	Screening chemistries and flocculent design or another novel approach for impurity removal					
		🟡	🟡	🟢	🟢	
Disruptive technology	Continuous/efficient selective removal of impurities with high yields and low process times; custom manufacture of green flocculants at commercial scale					
		🟡	🟡	🟢	🟢	
Need	Antigen-specific affinity approach/media providing for high-selectivity separations (e.g. resins, membrane, etc.)					Affordability, speed to market, supply chain robustness
Challenge	Complexity and diversity of antigen epitopes; consistent manufacturing of chromatographic resins for commercial manufacturing; access to ligand libraries; toxicity of ligand; costly multi-step chromatographic steps					
Potential solution	Develop epitope mapping approaches with associated media chemistries to develop robust ligand-media conjugation; reusable ligands; simplified process					
		🟡	🟡	🟢	🟢	
Disruptive technology	Single-step selective binding with a high binding capacity; media that are easy to clean and conjugate with the ligand; 'cleaning in place'-stable chemistries that do not leach					
		🔴	🟡	🟡	🟢	

Manufacturing Readiness Level

🔴	🟡	🟢
Research	Development	Manufacturing

Table 2: Drug substance process development – needs (continued)

		Current	3yrs	5yrs	10yrs	Impact
Need	DS activation/conjugation chemistries that are site-specific, efficient and universally applicable					Affordability, speed to market, supply chain robustness
Challenge	There is lack of platform chemistry applicable to a wide variety of capsular polysaccharide, small molecule and carrier protein structures					
Potential solution	Site-specific, bioorthogonal conjugation chemistry applicable to a group of target molecules					
		●	●	●	●	
Disruptive technology	Cell-based conjugation methodology					
		●	●	●	●	
Need	Alternate sterile filtration technologies for very large vaccine modalities					Affordability, speed to market, supply chain robustness, improved market accessibility
Challenge	Large vaccine modalities are retained by traditional sterile filtration and require non-ideal aseptic processing solutions					
Potential solution	Novel membrane technologies					
		●	●	●	●	
Disruptive technology	Novel, non-destructive sterilization technologies					
		●	●	●	●	
Need	Continuous manufacturing					Affordability, supply chain robustness
Challenge	Diversity of biological systems and production unit operations; product-derived cytotoxicity during fermentation/cell culture; in-process product stability, particularly for live viral vaccines					
Potential solution	Hybrid approaches (i.e. continuous fermentation/cell culture with batch-mode purifications); advanced process modeling and unit operation cycling					
		●	●	●	●	
Disruptive technology	Real-time, product quality-driven process advancement triggers for end-to-end continuous manufacturing					
		●	●	●	●	

Manufacturing Readiness Level

Research	Development	Manufacturing
●	●	●

3.3 Drug product process development

Vaccines are preventive products that are costly to produce and, in certain cases, the immediate value to individual patients may not be obvious. Vaccines are typically given to healthy individuals (often to prevent an infectious disease) for whom the full value of the disease prevention may not always be sufficiently tangible to incentivize full compliance with the necessary regimen. Vaccines can be given separately or in combination with other vaccines according to a complex immunization schedule over the lifespan of the patient, usually requiring a visit with a healthcare professional for each dosage.

Unfortunately, the burden of adhering to this vaccination schedule can lead to lower rates of compliance that undermine the individual and societal value of the vaccine. Therefore, a major need is to reduce the burden on patients, either through more convenient dosing schedules or more patient-friendly delivery systems. For example, a long-term goal would be to reduce immunization burden with an appropriate device while

maintaining and/or improving the safety profile. Vaccines that can be self-administered at home by the patient or a caretaker would reduce the burden on the vaccine administrator, especially in times of a pandemic. Therefore, there should be an emphasis on developing 'simpler' alternate delivery routes of administration (e.g. mucosal, transdermal, controlled-release) while developing stable combinations of vaccines for pediatric and adult populations.

A second major need is to reduce the cost of delivering vaccines to these patients. For many vaccines, each dosage requires an expensive, sterile cold-chain to ensure maintenance of a safe, effective and quality product for the entire shelf-life of the product. Healthcare professionals administer most vaccines, albeit in a variety of contexts ranging from individual patient care in clinics and doctor's offices to large immunization campaigns serving whole communities. The variability and complexity of bringing these products to patients impose significant inefficiencies and costs on the healthcare system. In addition to reducing the labor requirements for healthcare professionals by empowering patients as discussed above, two particular cost areas that need attention are the fill/finish process and storage and transportation of the DP.

Today, a substantial part of the CoGs is generated by the fill/finish operations as most of the vaccines are aseptically manufactured and delivered in vials (mono- or multi-doses) or syringes. Also, the fill/finish process has presented a significant bottleneck in recent pandemic responses [5]. Therefore, there is a need to increase both efficiency and throughput capacity in fill/finish processes. Promising routes for addressing this need in the short to medium term include continuing to develop and validate:

- decentralized fill/finish processes that reduce technology transfer time
- better aseptic fill/finish technologies (e.g. SU product contact parts, barrier isolators)
- less expensive blow-fill-seal container systems
- more cost-efficient individual containers that are easier and safer to use for healthcare professionals and patients
- continuous, straight-through manufacturing (e.g. DS to DP with continuous fill/finish and RTR).

Alternatively, a potential longer-term solution would be developing technologies that enable vaccine production in less stringent conditions and sterilization of the product without damaging its biologics or otherwise affecting its efficacy. One salient example would be the terminal sterilization of hepatitis vaccines.

Most current vaccines require strict cold-chain (2–8°C or below) storage and transportation as they are sensitive to warm temperatures and freezing conditions, as is the case with products containing adjuvants. These complex logistical requirements lead to a significant loss of product during the distribution path, especially in emerging countries. Accessibility for broader populations to immunization programs will necessitate the holistic improvement of the entire logistic path. Another way would be to develop new vaccine formulations and adjuvant toolkits that are robust and less sensitive to extended temperature excursions or are even totally thermostable.

See Table 3 for a list of vaccine product needs, challenges and potential solutions.

Table 3: Vaccine products – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Improve vaccination compliance					Improved vaccination rate
Challenge	Cumbersome dosing regimen reduces patient adherence					
Potential solution	Combination vaccines to reduce immunization dosing frequency					
		●	●	●	●	
Disruptive technology	Approaches for making combination vaccines (fixed dose vs. mix and match); vaccine patch; e-schedule/compliance app for smart devices					
		●	●	●	●	
Need	Improve vaccination rate and compliance					Improved vaccination rate, reduced cost
Challenge	Currently, vaccines are administered by healthcare professionals, typically in clinics or pharmacies					
Potential solutions	Non-invasive delivery routes, e.g. mucosal, transdermal, intradermal					
		●	●	●	●	
	Controlled release vaccines (e.g. sustained or pulsatile); patch technology					
		●	●	●	●	
Disruptive technology	Vaccine implants; patches; bioneedles; dose-sparing approaches; novel formulations with well-defined pharmacokinetics and toxicity profiles; adjuvants for improved efficacy					
		●	●	●	●	
Need	The inherent instability of vaccines with a lack of cold-chain limits the global accessibility of vaccines					Accessibility, reduced time and cost of quality, safe, innovative supply chain.
Challenge	Many vaccines require a cold-storage supply chain					
Potential solutions	Holistic logistical management and supply partnership management, e.g. distributed manufacture, more robust delivery options					
		●	●	●	●	
	Thermostable vaccine formulations; convenient devices with smaller footprints; advanced vaccine vial monitor approaches					
		●	●	●	●	
Disruptive technology	Fully thermostable vaccines; new vaccine modalities; adjuvants that can be freeze dried; formulations for global access					
		●	●	●	●	

Manufacturing Readiness Level

●	●	●
Research	Development	Manufacturing

Table 3: Vaccine products – needs (continued)

		Current	3yrs	5yrs	10yrs	Impact
Need	On-demand, high-volume/low-cost manufacturing of vaccines					Affordability, accessibility, time to market
Challenge	Aseptic fill/finish operations are slow and/or costly due to batch processing and long-lead analytical requirements					
Potential solution	Integration of more efficient aseptic technologies, e.g. SU product contact parts, barrier isolators solutions					
		●	●	●	●	
	Continuous manufacturing coupled with advanced process controls, including RTR; container systems that are both easy to blow-fill-seal and easy/safe to use					
		●	●	●	●	
Disruptive technology	Terminal sterilization; RTR; continuous lyophilization or alternate drying approaches					
		●	●	●	●	

Manufacturing Readiness Level

● Research ● Development ● Manufacturing

3.4 Analytical

Analytical tools for vaccine manufacturing are essential for developing robust and efficient biomanufacturing processes. Measuring molecular species during production is important, including dissolved gases, sugars, proteins, peptides and other components. Tools for these measurements can range from a seemingly simple in-line pH meter to sophisticated spectroscopic analysis or an at-line chromatography system. Manufacturing viral vaccines, such as live virus vaccines and viral vectors, requires the quantification of viral infectivity (i.e. the number of infectious viral particles per unit volume). Such quantitation is required at various points in the vaccine development process including; R&D, scale-up, biomanufacturing, formulations, release assays, clinical efficacy testing (neutralization assays).

Several needs have been identified in the short-, medium- and long-term horizons as discussed in table 4 below.

In the short term, an important capability is rapid and real-time infectivity monitoring as a process analytical technology (PAT). This would be a critical capability directly tied to production monitoring and ensuring the efficacy of the final product in many cases (e.g. live virus vaccines). The infectivity measurements should correlate with traditional infectivity assays, such as the plaque and end-point dilution ($TCID_{50}$) assays. However, novel approaches should also help to automate the process, provide a wealth of data for batch records and validation, and be able to provide quantitative results in a fraction of the time of current assays.

Similarly, for vaccines made in cells, (e.g. real-time cell-health monitoring) technologies that go beyond traditional viability studies would be important and should also be amenable to rapid and automated on-line sampling. In general, technologies need to comply with Title 21 Code of Federal Regulations Part 11 [4] to enable manufacturing traceability and also be good manufacturing practice (GMP)-compliant and compatible.

Over the medium-term development time frame, the real-time operability of analytical techniques is deemed critical, as is having more extensive in-line analytics and real-time models to better monitor and predict production. This capability would reduce or eliminate out-of-specification lots, greatly saving time and resources wasted by these failures. Some specific examples include the ability to automate the monitoring of virus-like

particles production in yeast, baculovirus, mammalian cells and other systems. The ability to use next generation sequencing is identified as important for quality control and adventitious agent characterization.

Longer-term goals include distributed control systems that are interconnected with in-line analytics through predictive models to better control and optimize processes. This should be coupled with high-throughput analytics that uses 'big data' and machine learning algorithms to best control and predict processes.

Another area identified as a need was PAT standards. Having standard materials and validation protocols for in-line stability, continuous processing, release assays and other operations would be advantageous for understanding and comparing various PAT methods and instruments. In-line monitoring and RTR, for example, would enable a substantial reduction in product release time (1–2 days compared to weeks–months). They would also improve the quality, efficiency and supply of the product through enhanced in-line monitoring, and indirect and multivariate sensors along with multivariate analysis and predictive modeling.

Table 4: Analytical – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Real-time infectivity monitoring					Improved efficiency and throughput
Challenge	Slow, error-prone infectivity measurements with high variability					
Potential solution	Rapid, quantitative, high-throughput, automated cell-based assays or other novel approaches for infectivity monitoring					
						
Disruptive technology	Laser force cytology; novel assay; engineered cell lines					
						
Need	Fast, accurate and robust process monitoring and characterization tools					Simplified process characterization; improved quality, efficiency and supply
Challenge	Complex batch processes; lack of a well-defined surrogate for process characterization (i.e. Certified Quality Attribute)					
Potential solution	Biomimetic assays; simplified continuous process with integrated automation/process monitoring and data management					
						
Disruptive technology	PAT tools and sensors; real-time assays with built-in feedback loops					
						
Need	Rapid DP release					Fast DP release; built-in quality, efficiency and supply
Challenge	Highly variable or long lead-time potency assays; batch-mode production/packaging					
Potential solution	Non-invasive release; mimetics; PAT sensors for product characterization and identification (e.g. moisture, spectroscopy; high-throughput, fast and automated release approaches; next generation sequencing; preliminary screening with a sensitive assay; Container Closure Integrity monitoring)					
						
Disruptive technology	Standardized PAT tools and sensors; alternate approaches to potency assays and sterility assurances; sensors for non-viable and viable particulate monitoring					
						

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Table 4: Analytical – needs (continued)

		Current	3yrs	5yrs	10yrs	Impact
Need	Immune correlate of protection enabling smart clinical trials					Fast DP release; built-in quality, efficiency and supply
Challenge	Need for better analytical metrics for vaccine efficacy and neutralization assays					
Potential solution	Cell-based assays or blood-based biomarkers					
		●	●	●	●	
Disruptive technology	Novel assays on blood biomarkers or cell-based attributes					
		●	●	●	●	

Manufacturing Readiness Level

● Research ● Development ● Manufacturing

3.5 Modeling

Mathematical models of individual unit operations and overall processes can be employed in process development as well as in manufacturing. In process development, such models, even if not of high predictive accuracy, can reduce the size of the parameter space to be explored experimentally. In manufacturing, process reliability may be aided by using models to explore the causes for excursions in the values of process variables and, in the longer term, may be employed when implementing process control structures and algorithms. The diverse range of vaccine modalities and the corresponding differences in their biophysical characteristics renders this a challenging task. Therefore, capturing sufficient detail to transcend conceptual validity and make actual quantitatively meaningful predictions, is the minimum required capability of the developed models.

Any of a variety of model types can be used productively. The ideal is often a fully predictive mechanistic model in which physically meaningful parameters can be varied to explore the effects of significant experimental 'handles', such as flow rate or column dimensions in chromatography. Such models remain rare. However, even for extensively studied operations such as chromatographic and membrane steps, active development of models is likely to change the landscape in the medium term. In these efforts, model discrimination and validation will be aided by high-throughput measurement and multivariate parameter estimation. In the long term, the sophistication of these models can be increased to allow the incorporation of molecular-level biophysical models and allow the predictive estimation of important parameters such as protein adsorption isotherms.

Because of the current immature nature of mechanistic models, a variety of empirical models are likely to be more widely employed in the short to medium term. The simplest of these may have their roots in the response surface methodology approaches that are widely used in practice, but when coupled with the advances in analytics, described in section 3.4 above, can greatly increase the sophistication of these methods. Specifically, high-throughput analytics can produce large repositories of data that allow the use of 'big data' methods, machine learning, artificial intelligence to develop powerful mechanistic models that can be coupled to existing methods to provide model-based predictive control. Such models are especially well suited for operations affected by large numbers of variables but with poorly understood mechanistic bases.

See Table 5 for a list of modeling needs, challenges and potential solutions.

Table 5: Modeling – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Predictive mechanistic models of individual unit operations					Speed in process development, facility/ automated development
Challenge	Capturing effects in sufficient detail to transcend conceptual validity					
Potential solution	Harness high-throughput measurement and multivariate parameter estimation in model discrimination and validation					
		●	●	●	●	
Disruptive technology	Digital twins; predictive determination of model parameter from structural (biophysical) information					
		●	●	●	●	
Need	Accurate prediction of long-term product stability using accelerated stability data					Quality, speed, flexibility
Challenge	Non-linear Arrhenius kinetics or multiple degradation or aggregation pathways; lack of data through the product lifecycle, reliably linking accelerated stability data with real-time stability/storage					
Potential solution	Improved mathematical models leveraging real-time data throughout multiple product lifecycles					
		●	●	●	●	
Disruptive technology	Adaptive models established through validated 'big data' analytics throughout the process of product development, storage, shipping and handling					
		●	●	●	●	
Need	Simplifying and accelerating technology transfer; eliminating and/or reducing the need for engineering runs					Speed, avoiding divergence, reduced discard, robust and reliable supply chain
Challenge	Diversity of unit operations between facilities and scales					
Potential solution	Suppliers providing well characterized design spaces and equipment capabilities under certain test conditions (e.g. lyophilization sublimation rates)					
		●	●	●	●	
Disruptive technology	Suppliers providing digital twins of their products and scale-up models					
		●	●	●	●	
Need	Correlating and understanding product attributes and their clinical relevance					Speed, cost, better patient outcomes
Challenge	Complexity, multiple modalities and cost of clinical design					
Potential solution	Experimental medicine studies; advanced mimetics					
		●	●	●	●	
Disruptive technology	Smart clinical trial or in vitro biomimetics; immune system on a chip; artificial intelligence; patient digital twins					
		●	●	●	●	
Need	Development of predictive models for product expression and quality					Speed to market, supply chain robustness
Challenge	Complexity and diversity of the unit operations and biological processes associated with vaccine manufacture					
Potential solution	Integrated multi-omics and multivariate data analysis approaches					
		●	●	●	●	
Disruptive technology	Toolkits for non-invasive, real-time omics analysis coupled with multivariate process monitoring					
		●	●	●	●	

Manufacturing Readiness Level

●	●	●
Research	Development	Manufacturing

3.6 Knowledge management

Advanced methodologies and utilization of product/process data and models should be considered as a cornerstone for a knowledge management system. Knowledge is often thought of as the final frontier of manufacturing capabilities.

The manner in which data and models are used is categorized under different types of analytics (not to be confused with PATs, as in Section 3.4). Descriptive analytics is the use of past performance data to better understand what may happen in the future. Predictive analytics takes this a step further and uses algorithms to predict future performance or outcomes. Finally, prescriptive analytics goes yet further by suggesting actions that would benefit the process goals. Therefore, the use of prescriptive analytics in biomanufacturing is a key component of future analytical capabilities desired for automated feedback and process control.

An example of an advantageous capability enabled with the introduction of advanced process analytics would be real-time data sharing and planning for a smart supply chain network. This would couple the production with the distribution chain to maximize the availability of medicines for both clinical trials and patients in need of vaccination.

See Table 6 for a list of knowledge management needs, challenges and potential solutions.

Table 6: Knowledge management – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Improved product/process information repositories to facilitate cross-company collaboration, standardization and scientific development to address common pain points					Cost, speed and quality
Challenge	Legal liabilities; proprietary intellectual property; lack of common vocabulary/taxonomy; potential for misuse/misinterpretation of data					
Potential solution	Open data-sharing of common non-proprietary product/process information					
		●	●	●	●	
Disruptive technology	Apply 'big data' analytics to public domain outcomes data					
		●	●	●	●	
Need	Lifecycle management of product/process information					Speed to market, product and drug quality
Challenge	Complexity of information; lack of applicability of product lifecycle management/knowledge management tools to the process industries					
Potential solution	A commonly implemented software package with feedback-loop alert capabilities					
		●	●	●	●	
Disruptive technology	A universal software package					
		●	●	●	●	

Manufacturing Readiness Level

●	●	●
Research	Development	Manufacturing

3.7 Workforce development

There are some companies involved in vaccine manufacturing utilizing different production systems. The novelty and complexity of these approaches (regarding R&D, clinical studies, technology transfer and commercialization, all with a focus on time-to-market, cost-effectiveness, scale-up of production, quality, safety/biosafety issues) require personnel at all levels that are knowledgeable and experienced. Lack of a well trained and readily available workforce can result in various bottlenecks for bringing therapies to market in a timely manner. It can also cause serious errors and omissions in the manufacturing process that can affect patient health and raise questions about vaccine safety and effectiveness.

A comprehensive training program on vaccine biomanufacturing is essential to help develop this workforce. The expected outcomes of this are technically proficient individuals with skillsets to create and follow standard operating procedures. The workforce will operate and monitor sophisticated equipment such as bioreactors, vaccine purification instrumentation and unit operations associated with various fill/finish operations (i.e. all aspects of DP development, including specialized unit operations such as drying, tangential flow filtration). At the same time the workforce will understand and apply regulatory guidance and GMP documentation. The emphasis of these training programs should be on high-quality vaccines produced under a highly regulated environment while maintaining cost effectiveness.

Please note, the timelines, lifecycle of vaccines and complexity/multiplicity of modalities and technologies generally surpasses that of biologics (e.g. antibodies) and therefore requires greater problem-solving capabilities, adaptability and diversity with improved depth and breadth of technical knowledge. Also, as the biopharmaceutical industry moves into the 'big data' era, the workforce will need to focus on both the development of a sound foundation in these data science methodologies as well as the integration of these approaches with biological and process science principles to realize their full potential.

A comprehensive vaccine biomanufacturing training program will need to cover these focus areas:

1. **cell culture techniques:** strategies for the growth of vaccine-producing cells in bioreactors and stationary systems; modern techniques used with animal cells in culture; microbial growth and recombinant vaccine production; hands-on execution of stationary cell culture; stainless steel fermenters; SU bioreactors with and without microcarrier culture
2. **biosafety issues:** pertaining to the handling of infectious agents and the manufacture of viral vaccines; waste inactivation; containment practices; personnel training and protection
3. **virology and vaccinology:** vaccines and the immune response following vaccination; virus cultivation; titration; assay validation; inactivation and stability testing of inactivated virus vaccines
4. **scale-up strategies:** methodologies used in the production of recombinant vaccines and animal cell-based vaccines taking into consideration process design and optimization; monitoring and control of the process from bench-scale to pilot-scale to production-scale and for the development and application of relevant scale-down models
5. **downstream processing:** practical skills to optimize separation and purification processes; in-depth presentations and laboratory work on the steps involved in the downstream processing necessary to create a finished product from cells in culture; hands-on execution of chromatography, normal and tangential flow filtration, precipitation, conjugation, centrifugation and novel technologies
6. **bioanalytics:** pertaining to the knowledge for the design and execution of common techniques for vaccine characterization; relevant knowledge of underlying theory with hands-on execution of analytical separations (e.g. HPLC/UPLC), gel-based methods (e.g. SDS-PAGE, capillary isoelectric focusing), mass spectrometry, immunoassays (e.g. ELISA) and cell-based methods (e.g. plaque potency)

7. **drug product:** experience of the design and execution of common DP unit operations; relevant knowledge of underlying DP theory (e.g. mixing, glass transition temperature, formulation components, aggregation, oxidation); hands-on design and execution of formulation, scale-up and technology transfer of various vaccine modalities, including recombinant protein, polysaccharide, mRNA and live virus along with (in special cases) device integration and evaluations (e.g. extractables and leachables, device performance)
8. **key regulatory issues:** phases of clinical development and considerations at each stage; the validation process and documentation; International Council for Harmonisation guidance; biologics license application sections and approval process; considerations for filing in global markets; accelerated review options (e.g. breakthrough designation, PRIME); post-approval changes and comparability
9. **key quality considerations:** good manufacturing practices for vaccine production; quality control and quality assurance in vaccine manufacturing; documentation practices; quality considerations for process development; deviations
10. **process development considerations:** general laboratory techniques; aseptic techniques; presentation of results; process modeling; PAT and applications
11. **data science and statistical analysis:** statistical power and 'design of experiments'; multivariate and 'big data' analytics.

See Table 7 for a list of workforce development needs, challenges and potential solutions.

Table 7: Workforce development – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Awareness of all facets of vaccine manufacturing, overall rationale for specific workstream and its corresponding impact on the process and/or product					Reduced discard, reduced turnover, improved people engagement and improved productivity
Challenge	Lack of easily accessible avenues for learning and case studies associated with vaccine manufacturing; disconnect between academic knowledge and floor understanding/ challenge during vaccine production; lack of deep vaccine knowledge/manufacturing process in the public domain					
Potential solution	Specific training overviews of key topics (currently occurs within individual companies, no universal standard curriculum); greater exchange between industry and academia for knowledge sharing and knowledge gap analysis; facility location close to academic hubs with accessible training for students and scientists					
		●	●	●	●	
Disruptive technology	Vaccine-specific student/industry exchange program; industrial sabbatical programs for academic leads; seminar/industry podcast and guest lectures; hands-on exposure to laboratory and pilot-scale equipment (e.g. SU technology, lyophilization training); integrated cross-functional training providing an end-to-end review of vaccine manufacturing					
		●	●	●	●	

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Table 7: Workforce development – needs (continued)

		Current	3yrs	5yrs	10yrs	Impact
Need	A workforce that is well trained to work in a highly regulated GMP environment					Reduced discard, reduced cost, reduced cycle time, improved productivity
Challenge	Current entry-level workforce (0–5 years of experience) lack practical knowledge and skillset to bring vaccine products to market; limited participation in open forums by industry and regulators about lessons learned and case studies					
Potential solution	Work with national organizations to establish applicable training programs in vaccine manufacturing at universities; fundamental GMP courses (e.g. process/component and people flows for a given facility/BSL)					
		🟡	🟡	🟢	🟢	
Disruptive technology	Green room training with virtual reality (e.g. simulators, smart glasses); US Food and Drug Administration case studies and engagement documenting the challenges/observations for the workforce; joint ventures between vaccine manufacturers for fundamental training; retraining certificate course for non-subject matter experts					
		🟡	🟡	🟡	🟢	
Need	Training tools that are adaptive to population behaviors and next-generation workforce					Reduced discard, reduced cost, reduced cycle time
Challenge	Population diversity can reduce training efficiency/effectiveness of standardized training tools					
Potential solution	Virtual reality simulator training tools					
		🔴	🟢	🟢	🟢	
Disruptive technology	Incorporate training in big/smart data and machine learning into the curriculum; gamification of educational and training courses					
		🔴	🔴	🟡	🟢	

Manufacturing Readiness Level

🔴	🟡	🟢
Research	Development	Manufacturing

3.8 Regulatory and science standards

Improving vaccine affordability and accessibility through the robust and reliable supply of vaccines that leverage the technology revolution will need to be supported by clear regulatory pathways.

See Table 8 for a list of regulatory and science standards needs, challenges and potential solutions.

Table 8: Regulatory and science standards – needs

		Current	3yrs	5yrs	10yrs	Impact
Need	Advanced manufacturing with new technology integration (e.g. flex on-demand or continuous unit operations)					Speed to validation, cost
Challenge	Advice needs to evolve in parallel with the evolution of technology					
Potential solution	Continuing the discussion with regulatory bodies; partnering with the US Food and Drug Administration to develop open workshops for flex on-demand manufacturing and/or training in emerging technologies					
						
Need	Expanded guidelines for the qualification of master and working banks, as well as commonly used carriers and conjugates; global harmonization to the extent allowable by laws of the respective national regulatory authorities					Speed to market, cost
Challenge	Diversity of regulatory expectations across markets, as well as country-specific laws and regulations that bind respective national regulatory authorities; emerging risks and advancing technologies (e.g. adventitious agents, genetic stability)					
Potential solution	Improved alignment through International Council for Harmonisation and other international bodies that may have a regulatory impact (e.g. World Health Organization or European Medicines Agency)					
						
Need	A clear regulatory framework for product-agnostic early engagement and advice on incorporating new technologies into manufacturing processes					Speed, cost
Challenge	Guidance process is data-driven and not generated in parallel with new technology					
Potential solution	Advice provided in the context of early engagement is necessary; early engagement facilitated by a well communicated process for seeking technology advice (product-agnostic) from the Center for Biologics Evaluation and Research					
						

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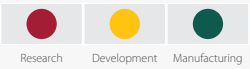

4.0 Conclusions and key recommendations

4.1 Conclusions

Vaccines are one of the greatest public health success stories and their globalization is not just a business necessity but also a public health obligation. The long-term vision for the future growth of this important, vibrant and fast-changing industry will be enabled by the various imperatives outlined in this roadmap. A few high-level desired goals are:

1. **process:** process intensifications; continuous manufacturing and advanced process controls (both predictive and prescriptive); closed-process production approaches
2. **product:** product design that allows on-demand manufacturing (e.g. a continuous straight-through process); thermostable products; lower CoGs; non-parenteral delivery; combination therapy that is affordable and accessible besides being a safe, effective and quality product
3. **analytical:** real-time, in-line and at-line monitoring and characterization eventually leading to RTR and prescriptive analytics
4. **modeling:** simplified technology transfer, prescriptive process control and stability profiles; facility lifecycle; predictive maintenance plan
5. **knowledge management:** integrated systems that allow knowledge and quality built throughout the lifecycle of the product
6. **facility:** an agile, automated fit-for-purpose flexible design with streamlined validation options for scale-up and scale-out
7. **regulatory science and standards:** modality-specific, 'chemistry, manufacturing and controls' guidelines; expedited protocols for new assay improvements to enable mechanistic approaches over traditional approaches; PAT standards expected for enabling validation (+/- tolerances); protocols for in-line stability; continuous processing and real-time DP release of vaccine products; guidelines for enabling new DP technologies and implementation
8. **workforce development:** industry, regulatory agency-engaged and academic-led educational programs and professional training programs.

4.2 Key recommendations

Benefits to biopharmaceutical manufacturing can be obtained by addition of various disruptive technologies and approaches mentioned here over the long-term horizon. Key conclusions and recommendations are:

1. continued investment in vaccine innovation (pipeline to address new infectious diseases, robust, reliable supply with low CoGs while enabling safe, effective and quality products) to address aging population and birth cohorts globally
2. simple and clear regulatory pathways especially for enabling novel, innovative approaches for vaccine process, analytical and formulation with newer facility design
3. open innovation: a sustained collaboration among industry, suppliers, regulators and research communities.

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Acronyms/abbreviations

ACF	Animal component-free
BSL	Biosafety Level
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CD	Chemically defined
CD-ACF	Chemically defined, animal component-free
CoGs	Cost of goods
DP	Drug product
DS	Drug substance
ELISA	Enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
GMP	Good manufacturing practice
HPLC	High-performance liquid chromatography
mRNA	Messenger Ribose Nucleic Acid
PAT	Process analytical technology
R&D	Research and development
RTR	Real-time release
SDS-PAGE	sodium dodecyl sulphate polyacrylamide gel electrophoresis
SU	Single-use
$TCID_{50}$	Tissue culture infective dose 50
UPLC	Ultra-performance liquid chromatography

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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Since its inception in 2004, the BioPhorum Operations Group (BioPhorum) has become a trusted environment where senior leaders of the biopharma industry come together to openly share and discuss the emerging trends and challenges facing their industry. The strong cross-company relationships built through BioPhorum have provided the solid foundation from which highly effective collaborations have grown, each focusing on key operational challenges, improving competitiveness and reducing patient risk. As well as the Technology Roadmap, BioPhorum runs six other Phorums – Drug Substance, The Development Group, Fill Finish, IT, Supply Partner and Cell & Gene Therapy. You can find out more at www.biophorum.com.

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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.

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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.