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White Paper

Modeling the Economics of Vaccine Manufacturing

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The unprecedented speed at which vaccines were developed against SARS-CoV-2 and their success in protecting against infection and mitigating symptoms reinforced their value against a wide range of infectious diseases. A renewed focus on vaccines and their broad utility, along with advances in production technologies, is leading to a significant expansion of their development and manufacturing. There is a wide range of vaccine modalities that can be leveraged, each having its own set of advantages, disadvantages, and production costs. To determine which is best for a particular application, it is essential to understand, evaluate, and optimize costs to maximize production efficiency. This white paper describes the use of a custom-designed cost model to explore the economics of vaccine manufacturing when using different modalities.

Vaccine Modalities

Vaccines have been essential for human health starting with the use of cowpox virus to confer protection against smallpox in 1796 by Edward Jenner. Since that time, this modality has evolved to include a broad range of approaches from inactivated viruses to viral vector vaccines, recombinant proteins and subunits, virus-like particles, and mRNA (Figure 1).

Vaccines which use **inactivated and attenuated** viruses to elicit immunity dominated the market in 2022 in terms of revenue (~34%) and represent approximately 16% of global vaccine development pipelines.[1]

Recombinant techniques enabled development of vaccines based on a partial structure of the pathogen such as proteins or polysaccharides to create a protective effect. By using highly purified antigens, these **protein subunit vaccines** eliminate the risk of administering viral material which could trigger the disease itself.

A type of recombinant protein subunit vaccine makes use of **virus-like particles (VLP).** The VLP structure contains repetitive, high density displays of viral surface proteins to elicit strong immune responses. In addition to robust efficacy and safety, this approach offers a great deal of flexibility for vaccine developers as multiple antigens can be presented on the surface of the particle.

Viral vector vaccines use a harmless virus to transport instructions for making antigens from the disease-causing virus into cells, triggering protective immunity.

Nucleic acid vaccines, including plasmid **DNA (pDNA)** and **mRNA**, are among the newest modalities. pDNA vaccines are based on purified plasmid preparations containing one or more DNA sequences capable of inducing and/or promoting an immune response against a pathogen. pDNA is also used in the production of mRNA vaccines. In mRNA vaccines, an mRNA target antigen sequence is delivered into the cytosol of a cell, inducing production of a target protein which triggers an immune response for vaccination purposes. mRNA vaccines can also be produced without the need for pDNA via a purely synthetic route.

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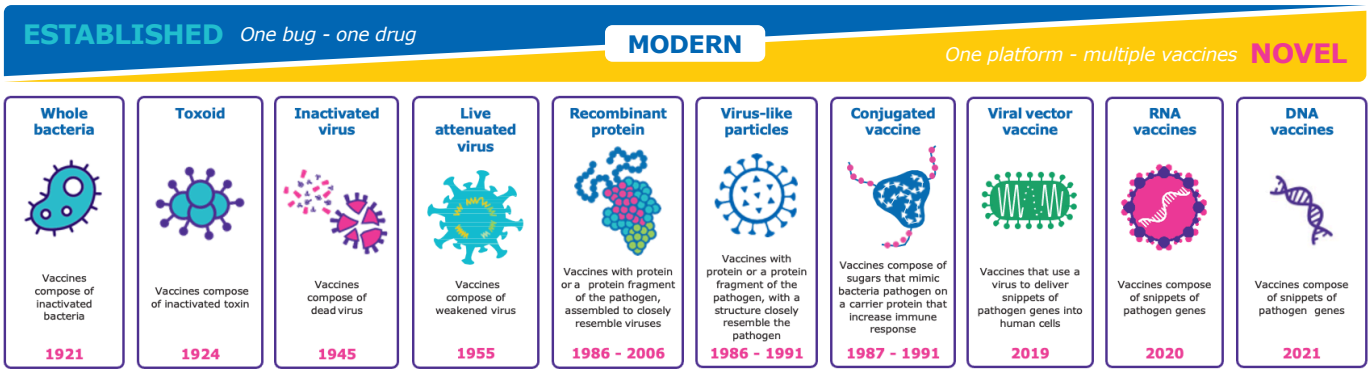

Figure 1. Vaccines range from established approaches that focus on single infectious agents to today's modern approaches developed using platform technologies.

Introduction to Cost Modeling

As vaccine developers pursue new indications and seek to establish robust, templated manufacturing workflows, cost modeling is a powerful tool to better understand processes, simulate bottlenecks, and optimize production efficiency. Cost modeling considers direct and indirect costs across the manufacturing process, from research to GMP manufacturing. Other costs such as R&D, marketing and licensing, packaging, distribution, would be separate from the modeling calculation, as these costs can vary significantly depending on each product.

With use of detailed modeling, it is possible to determine the cost to manufacture a vaccine using different modalities and how decisions related to the process such as scale and specific technologies can impact these costs. Cost modeling can also provide valuable guidance related to facility design for engineering teams.

Cost modeling can be applied throughout the vaccine manufacturing process to understand and identify the biggest cost contributors to the process. Sensitivity and what-if analyses can be performed to determine the cost impact of changes to demand and titer, and whether bottlenecks will be introduced by these changes. Models can also be used to run scenario simulations and evaluate proposed process changes on overall costs, quantify tradeoffs, quantify how costs shift with increased scale, and whether there may be limitations in equipment. Simulating process scheduling to optimizing facility and labor scheduling is also possible.

Cost modeling does have limitations, however. It can't predict if the given approach will work from a technical standpoint and does not use absolute costs with high accuracy. Cost models cannot address elements of uncertainty including market changes, acknowledged and mystery unknowns, and the potential impact of technical innovations. As market dynamics and technology evolve, cost models require regular calibration to remain relevant.

Building the Vaccine Cost Model

This whitepaper describes the development and use of a cost model encompassing capital, labor, materials, consumables, and other costs, which are five key parameters of manufacturing for a variety of vaccine modalities (Figure 2). Manufacturing costs, which reside between the lengthy and highly variable costs of process development and commercialization, are more easily defined and therefore more amenable to being assessed via cost modeling.

The model was developed using BioSolve software (Biopharm Services) and was based on inputs related to the process flow and parameters, cost of materials, and other assumptions. Model inputs were based on published information; mass/material balances, sizing for consumables, and equipment were based on anticipated process volumes, along with time, labor, floorspace, and utilities to calculate the cost of manufacturing, capital expenses, and the relevant bills of material.

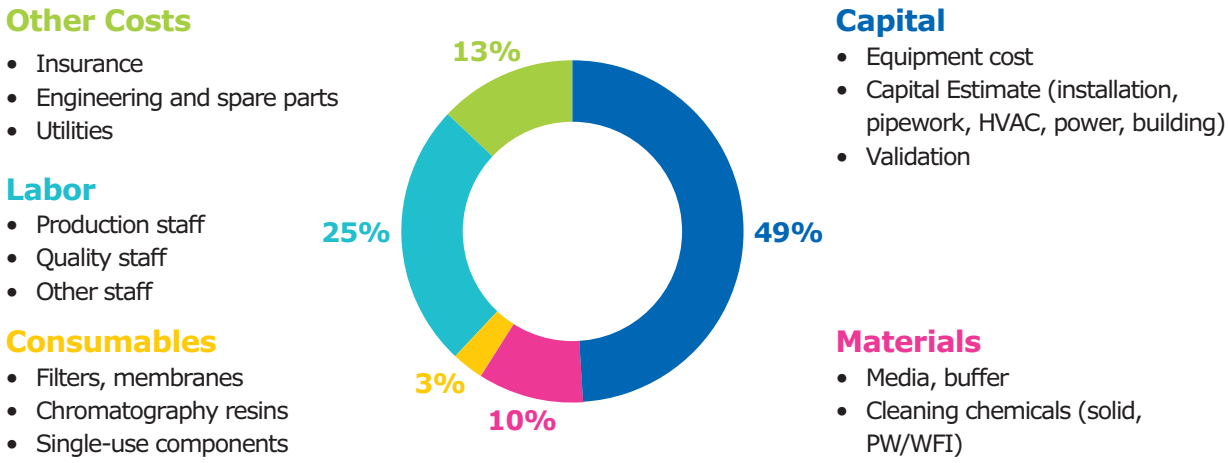

Figure 2. Manufacturing-related parameters included in the cost model.

Cost Modeling Objectives

The objective of this initiative was to analyze and compare the cost structures and operational effectiveness of producing a range of vaccine modalities from the more traditional to those on the leading edge of innovation. The model was also used to reveal steps that might be possible bottlenecks based on the contribution to overall costs, and to explore the impact of legacy processes and single-use technologies on the cost structure.

Results: Cost-per Dose Comparison of Single-Use and Legacy Manufacturing Technology

Figure 3 provides a cost comparison of stainless steel and single-use processes. Cost per dose was generally higher using stainless steel equipment, mainly due to the much higher cost contributed by capital investment and labor, which overshadowed the savings on consumables and materials. Labor costs included a range of activities such as steam-in-place and cleaning-in-place procedures, buffer preparation, and validations. While a lower utilization rate increased the impact of capital cost, simulation of scenarios can be used to identify an optimized alignment of cost savings and production efficiency.

The cost distribution for a legacy process and single-use process under low and high facility utilization rates is shown in **Figure 3** for inactivated and protein subunit viruses, two common modalities used in marketed products.

Cost distribution among legacy process and single-use process were compared under low and high facility utilization rates. As shown in Figures 3A and 3B, the modern single-use process had a lower overall cost per dose, due to a reduction in labor and capital and a higher yield in modern single-use processes. As a result, the batch number was lower for the single-use process which translated to lower consumables cost. A comparison of the modern protein subunit processes in Figures 3C and 3D demonstrated that the yield was the same for both legacy and single-use processes. As the facility utilization rate increased to 80-90%, the cost per dose was comparable; there was a reduction in capital and labor cost for the single use process and a higher percentage of consumables costs (3D).

The single-use process has a lower overall cost per dose, due to a reduction in labor and capital and a higher yield from this more modern process for production of inactivated virus vaccines (**Figure 3A and B**). This results in a smaller number of batches and thus the lower consumable cost. For protein subunits, the yield is the same for both legacy and single-use processes (**Figure 3C and D**). As the facility utilization rate increased to 80-90%, the cost difference was reduced and nearly comparable. The cost for consumables, however, was higher while capital and labor were lower in the single-use processes.

Predicting demand for a vaccine can be difficult, leading to changes in facility output and utilization. Single-use technology offers a more flexible approach for meeting demand and reducing the initial capital spend, while maintaining a low cost of goods. Subsequent data sets focus on single-use processes and an mRNA platform; a 10M annual dose production volume was used to compare costs across different vaccine modalities

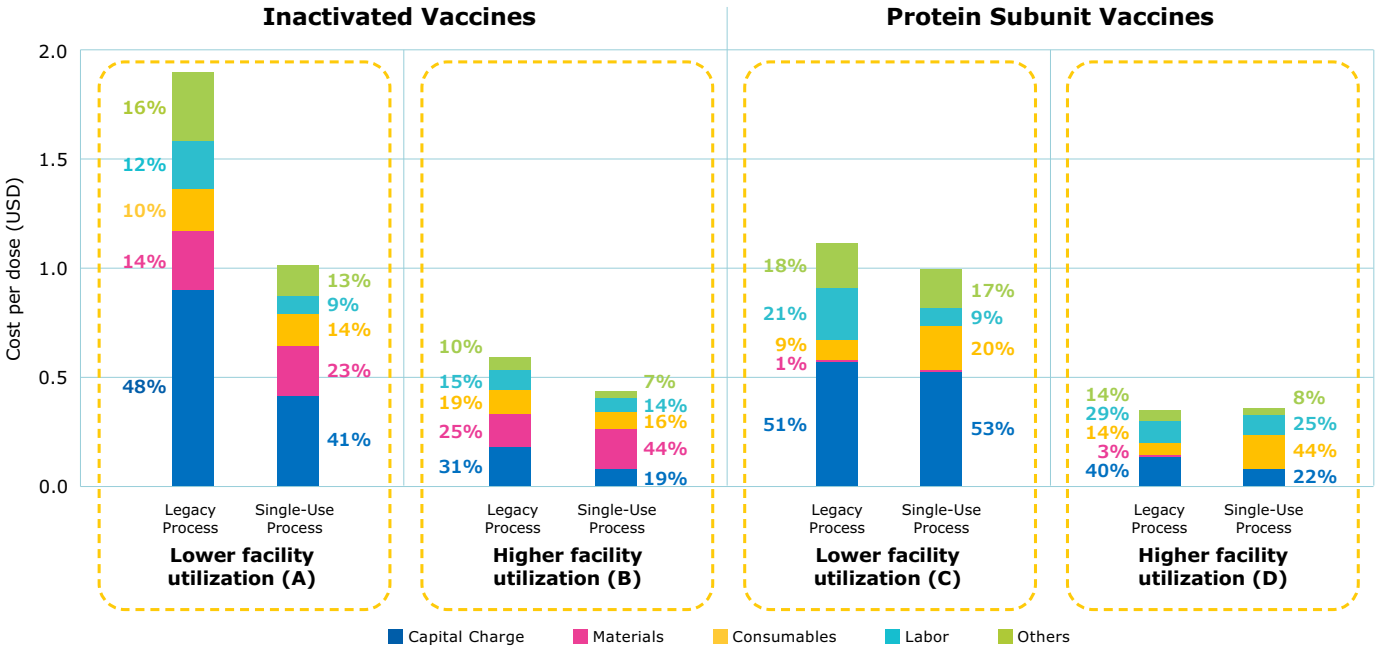

Figure 3. Cost per dose comparing legacy stainless steel processes and single-use processes at commercial scale.

Results: Cost of Goods based on Vaccine Modality

Figure 4 shows the cost per dose by modality at commercial scale productions with fully single-use processes. For all modalities, labor costs averaged close to 10% and the contribution of consumables, such as chromatography resin or single-use materials, increased as the number of batches increased. As shown by the results, overall cost per dose was highest for mRNA vaccines, followed by traditional Inactivated vaccines, protein subunit vaccines, and virus-like-particle vaccines.

Inactivated vaccines have similar costs related to materials and consumables; capital expenses represent about one-third of the total cost. VLP vaccines produced using insect cell systems have lower consumable costs due to higher titers and fewer batches being needed to achieve the same annual dose volume requirement compared to CHO cell-based protein subunit platforms. mRNA vaccines had the lowest capital and labor costs, due to having the smallest production footprint and a simpler processing workflow.

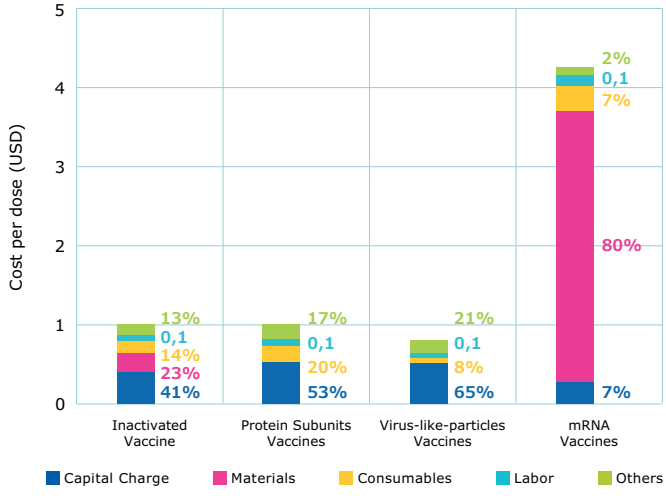

Figure 4. Percent contribution of individual costs and cost per dose by modality at commercial scales.

Results: Contribution of Unit Operations to Overall Cost

The model was next used to identify the cost of each unit operation for different vaccine modalities. **Figure 5** compares the cost structure of inactivated and mRNA vaccines as an example. When considering overall manufacturing cost distribution, the capital charge for inactivated vaccines is approximately 41%, compared to 7% for mRNA vaccines; material cost is approximately 23% for inactivated vaccines and 81% for mRNA vaccines. The difference in cost distribution reflects the fact that initial capital expenses, the scale of hardware systems, and facility footprint are higher with inactivated vaccines, compared with mRNA vaccines. With mRNA vaccines, most of the cost results from materials required for day-to-day operation.

The costliest operations in the mRNA process are plasmid linearization, transcription, and enzymatic reaction steps, while other costs are relatively minimal. With inactivated vaccines, use of endonuclease to digest host cell DNA is costly and increases the overall cost. Understanding the impact of various unit operation helps direct attention to the areas of the workflow which can be further optimized to reduce costs.

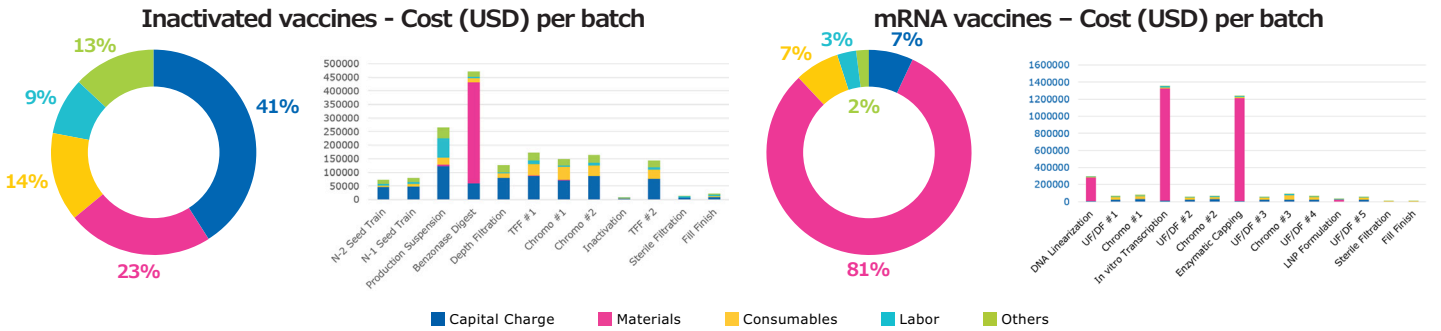

Figure 5. Comparison of cost distribution among major unit operations for inactivated and mRNA vaccine modalities.

Results: Contribution of Materials and Technologies to Overall Cost

Figure 6 shows the contribution of different materials and technologies including cell culture media, biopharma material, clarification, chromatography, ultrafiltration, virus filtration, aseptic filtration, single use bags and tubing; capital expenses and labor were not included. This analysis provides insight into which technology offers the best opportunity for optimization and cost reduction.

Single-use consumables were the largest cost contributors, for example, ranging from 45% to 90% depending on the modality. Costs of processing materials, such as endonuclease enzymes, were the biggest contributors for virus-based vaccines for day-to-day operations.

For protein subunit vaccines and VLPs, the cost for chromatography and clarification filters stands out. For mRNA vaccines, biopharma materials represent more than 90% of operating costs. To reduce costs for producing mRNA, less expensive enzymes or nucleotides could be used. Alternatively, the mRNA vaccine dose could be reduced using self-amplifying mRNA; with a lower overall dose volume, cost per dose can be reduced.

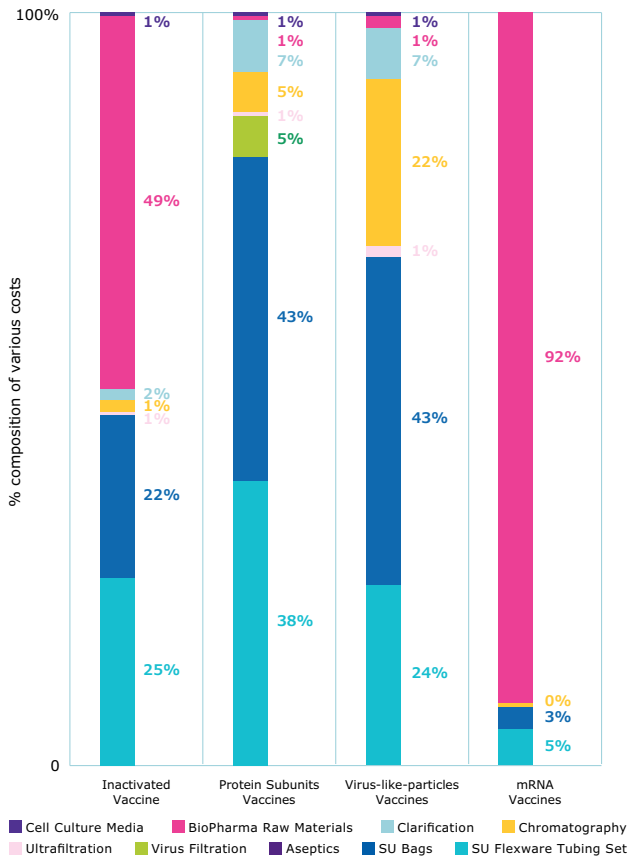

Figure 6. Comparison of cost of goods for materials and consumables in routine manufacturing.

Qualitative and Quantitative Comparison of Modalities

In addition to cost modeling, several qualitative and quantitative aspects related to the production of different vaccine modalities should be considered when choosing a development path (Table 1).

For example, inactivated vaccines have an excellent regulatory record, good product stability, process development is relatively straightforward, and the immunogenicity mechanism is well understood. These vaccines can, however, pose a risk for reverse virulence, creating a greater biosafety hazard for operators and thus increasing the complexity of the production facility.

Modern vaccines such as protein subunits and VLPs use well-characterized antigens and thus offer a safety advantage compared to traditional inactivated or live-attenuated vaccines. Process development can be rapid, if the antigen is defined and there are a variety of expression systems from which to choose (e.g., bacterial, yeast, mammalian cells, insect cells). Efficacy is typically high with the help of an appropriate adjuvant, and the side effects can be minimized. The cost of goods is generally comparable to traditional vaccines, but lower than mRNA vaccines. Facility complexity is reduced, and the approach offers more flexibility and shorter production time.

In terms of vaccine development speed, nucleic acid-based vaccines are the fastest. As an established platform technology, mRNA also enables a tremendous amount of manufacturing flexibility and production speed. In routine, large-scale manufacturing, mRNA vaccines would require the least costly capital installation to produce the same amount of target volume. With the same scale, mRNA technology can be used to easily produce many more doses compared to that of an inactivated vaccines production line. These vaccines also require the least facility utilization, thus leaving room for multi-vaccine production. mRNA is nevertheless a new modality, and evolving regulatory guidelines can create uncertainty.

Modality	Development Speed	Flexibility	Production Duration (batch)	Cost per Dose (USD)	Stability	Selling Price (USD)	Biosafety Hazard to Personnel	Facility Complexity	Adjuvant
Inactivated vaccine	++	+	+++	++	+++	+	High	High	Yes
Protein subunit vaccine	+	++	++	+	++	++	Medium	Medium	Yes
Virus-like particles (VLP) vaccine	+	++	++	+	++	++	Medium	Medium	Yes
mRNA vaccine	+++	+++	+	+++	+	+++	Low	Low	No

Table 1. Comparison of different vaccine modalities.

* Production duration per batch in this model study in days.

The scale of production and facility utilization also impacts the cost structure of vaccine manufacturing as illustrated by the cost model scenario simulation (**Figure 7A**). There were dramatic differences in the cost of production across Phases 1, 2, 3, and commercial scale for the different vaccine modalities. In Phase 1, small doses are produced using expensive equipment and as such, most costs are with fixed capital charges. As production is scaled, however, material and consumables costs became drastically higher (**Figure 7B**). In real-life situations, clinical materials are often produced in multi-product facilities or outsourced, thus sharing and reducing the absolute cost of capital and labor.

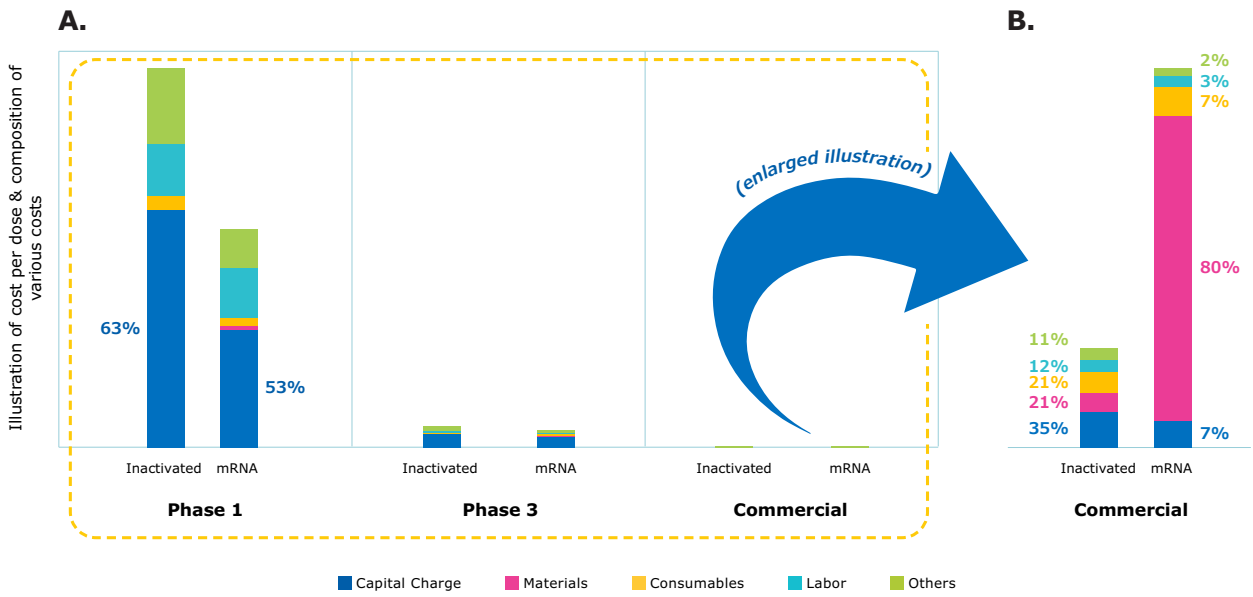

Figure 7. Comparison of cost structure in different manufacturing scales from clinical development to manufacturing.

Conclusion

The vaccine industry continues to grow and evolve. The speed at which vaccines were developed against SARS-CoV-2 and their success protecting against infection and mitigating symptoms reinforced their value and potential against a wide range of infectious diseases, cancer, and other conditions. It also inspired the pursuit of approaches to further accelerate the production of safe and effective vaccines.

As the industry seeks to accelerate workflows, intensify production, and apply more flexible approaches to vaccine manufacturing, cost modeling can be a powerful tool for understanding and optimizing processes. The model described in this whitepaper has been used to identify bottlenecks, simulate the effect of changes, and maximize production efficiency, among other applications.

Combined with a qualitative and quantitative assessment of the production parameters associated with different modalities, a cost model can offer important insights for determining which vaccine type is best suited for a particular application.

For example, the platform technology and flexibility of mRNA-based vaccines, when manufactured using single-use equipment, require the least capital investment. The smaller production scale reduces the facility design complexity, and lower utilization rate means that more doses can be produced per batch. As such, this vaccine modality can be a robust starting point for production with low risk.

Ultimately, selection of which vaccine modality will be produced requires cost considerations along with an assessment of available resources. In addition to applying a robust cost model, partnering with a technology provider with global experience in manufacturing all different types of vaccine modalities can further ensure a cost-effective, high-quality process.

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Spotlight on mRNA Vaccines

The use of mRNA for the production of vaccines was brought into focus by the proven victory of Moderna and BioNTech in the COVID vaccine race during the COVID-19 pandemic. As a result, there has been a great deal of investment in the development of mRNA-based vaccines and major clinical readouts on the horizon in areas of high unmet medical need.[2] While the cost of mRNA is the highest among other vaccine modalities as shown by the cost model described in this paper, efforts are ongoing to improve the efficiency of production.

Various global organization, local governments, and biopharmaceutical companies have initiatives centered on mRNA technology. For example, the Coalition for Epidemic Preparedness Innovations (CEPI) and the UK government recently hosted a Global Pandemic Preparedness Summit to explore how the world can respond to the next "Disease X", by making safe, effective vaccines within 100 days. CEPI is also partnering with SK Bioscience[3] to advance mRNA vaccine technology to enable a more rapid response to a possible pandemic. The Japanese government is investing in technology to ensure vaccines can be produced in 100 days[4]. Another example is the World Health Organization's (WHO) mRNA vaccine technology transfer hub, established to build capacity in low- and middle-income countries to produce mRNA vaccines. Sanofi's acquisition of TranslateBio[5] highlighted the focus of classical large pharma, which fast tracks establishment of Sanofi's recently announced mRNA Center of Excellence. Another example of a large pharma partnering with a smaller mRNA biotech company can be seen with GSK and CureVac and their joint development of second-generation mRNA vaccine candidates.[6]

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