EXECUTIVE INSIGHTS

Creating Value in Vaccines

The COVID-19 pandemic drove unprecedented demand for vaccine development and commercialization. Efforts such as Operation Warp Speed in the U.S., other ex-U.S. government programs and global private investment facilitated the entry of new and existing pharmaceutical products to fight infectious diseases.

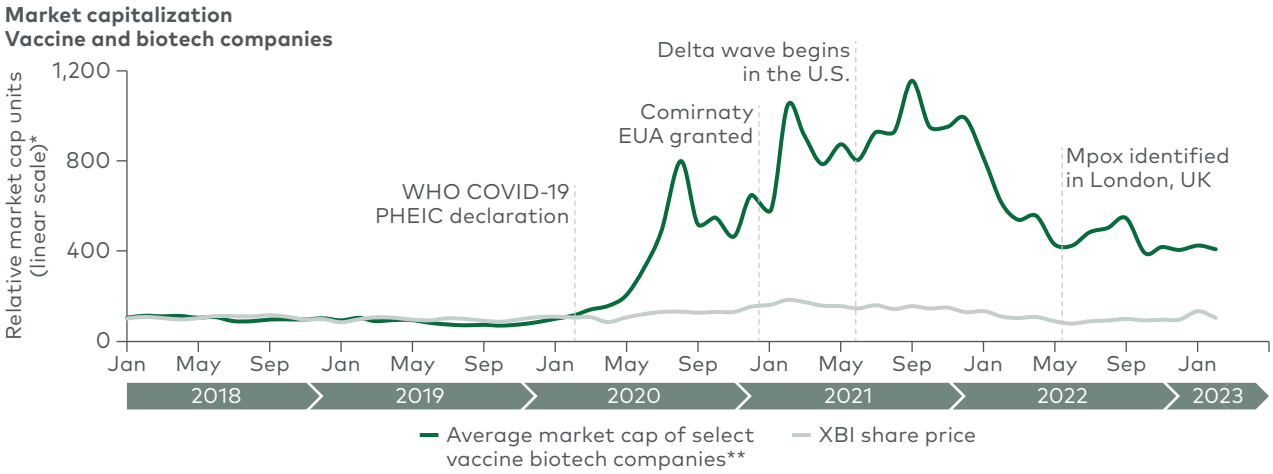
The valuation of vaccine companies skyrocketed after the World Health Organization (WHO) declared a public health emergency in January 2020, peaking at a more than tenfold increase in value by September 2021 compared to January 2018. The drastic increase in perceived value significantly exceeded that seen for the overall biotech sector, which doubled during that period.

As a result of this growth, many biotech and pharmaceutical leaders were increasingly likely to consider entering the vaccine space in order to capitalize on this prevailing interest and investment. While the overall biotech sector has lost considerable value since its 2021 peak, the even more precipitous drop experienced by most vaccine companies highlights the challenge in driving sustainable value creation in the vaccine space (see Figure 1).

Of the more than 450 different vaccine candidates that entered development to prevent COVID-19, only five have been approved across major markets and only two, Comirnaty and Spikevax, have driven sustained growth in shareholder value. The fact that only two out of more than 450 vaccines being developed have to date demonstrated sustained commercial success — despite the deployment of emergency use authorizations (EUAs) and unprecedented public funding and collaboration — underscores the myriad challenges and barriers that companies face even after successfully developing a vaccine.

In this *Executive Insights*, L.E.K. Consulting assesses the challenges associated with the vaccine market and what is required for a new or recent entrant to succeed.

Figure 1
Although the overall biotechnology market has remained relatively flat, the vaccine space saw sharp spikes and declines during the COVID-19 emergency



*Market cap of each company or index value set to 100 as of January 2, 2018, or earliest market cap available on S&P Capital IQ, whichever is later — numbers are calculated on the first trading day of each month
**Consists of the relative value of 16 vaccine companies averaged without weighting — companies are excluded prior to market cap availability
Note: WHO=World Health Organization; PHEIC=public health emergency of international concern; EUA=emergency use authorization; CDC=Centers for Disease Control and Prevention
Source: S&P Capital IQ; CDC; L.E.K. research and analysis

The vaccine space is complex and challenging

In the excitement to participate in the vaccine space, emerging, mid-cap and large pharmaceutical companies underestimated the unique challenges present in the market. Not recognizing or adapting to the differences between therapeutic and prophylactic vaccines can quickly lead to development, regulatory and/or commercial failure. We identified four key challenges that vaccine developers must address to ensure success (see Figure 2).

The barriers to success in the vaccine space, particularly within infectious diseases, stem from the challenges of vaccinating a large, healthy and global population. Regulators such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are reluctant to approve a vaccine in the absence of a clear and convincing risk-benefit ratio. Obtaining this data is difficult, as rare side effects may only be observed after inoculating many patients.

Figure 2
Summary of vaccine challenges

Source: L.E.K. research and analysis

Vaccine developers need to design trials with large, diverse sample sizes to ensure all possible rare adverse events and comorbidities are captured. These trials can be lengthy and costly, impacting both development timelines and return on investment. In addition, in the case of seasonal vaccines, there are often annual regulatory requirements that create additional development and regulatory costs as well as operational burdens for vaccine companies.

Policymakers such as the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) in the U.S., the National Advisory Committee on Immunization (NACI) in Canada, the Joint Committee on Vaccination and Immunisation (JCVI) in the U.K., the Technical Committee on Vaccinations (CTV) in France, and other advisory boards assess not only safety and efficacy in making their recommendations but also cost-effectiveness. A positive recommendation from these organizations is a prerequisite for high uptake.

Other market stakeholders that influence uptake include governments, physicians, pharmacies, distributors and patients. The level of influence of these diverse market stakeholders on vaccine uptake, pricing and access may differ by market or geography. In many high-income countries, retail pharmacies have gained increasing influence, creating additional pricing pressure and another layer of stakeholders for vaccine manufacturers to navigate.

The high-volume development, global commercialization, and associated tight and unpredictable operational timelines (e.g., seasonality, guidance windows, regional complexities) illustrate that developers must have access to both flexible manufacturing at scale and regional distribution networks.

Regulator preferences on strain selection and number of strains (e.g., monovalent vs. bivalent) included in a vaccine also can stress various parts of a biopharma company. R&D and commercial teams must be able to predict and develop updated versions of vaccines on a regular basis, while manufacturing capacity may need to be left idle when off peak. A diversified manufacturing and supply network, while not easy to come by, provides the flexibility needed to update, scale and distribute to the different stakeholders across markets in a timely manner.

In a competitive marketplace, new entrants may have a harder time creating necessary manufacturing and supply networks, resulting in likely tech transfer challenges as well as development and distribution delays. Additionally, keen oversight of the supply and manufacturing network, no matter how large or small it may be, is paramount. As was clearly illustrated during the COVID-19 pandemic, millions of vaccine doses had to be discarded due to a manufacturing error that led to the contamination of two vaccines being made in the same contract development and manufacturing plant.

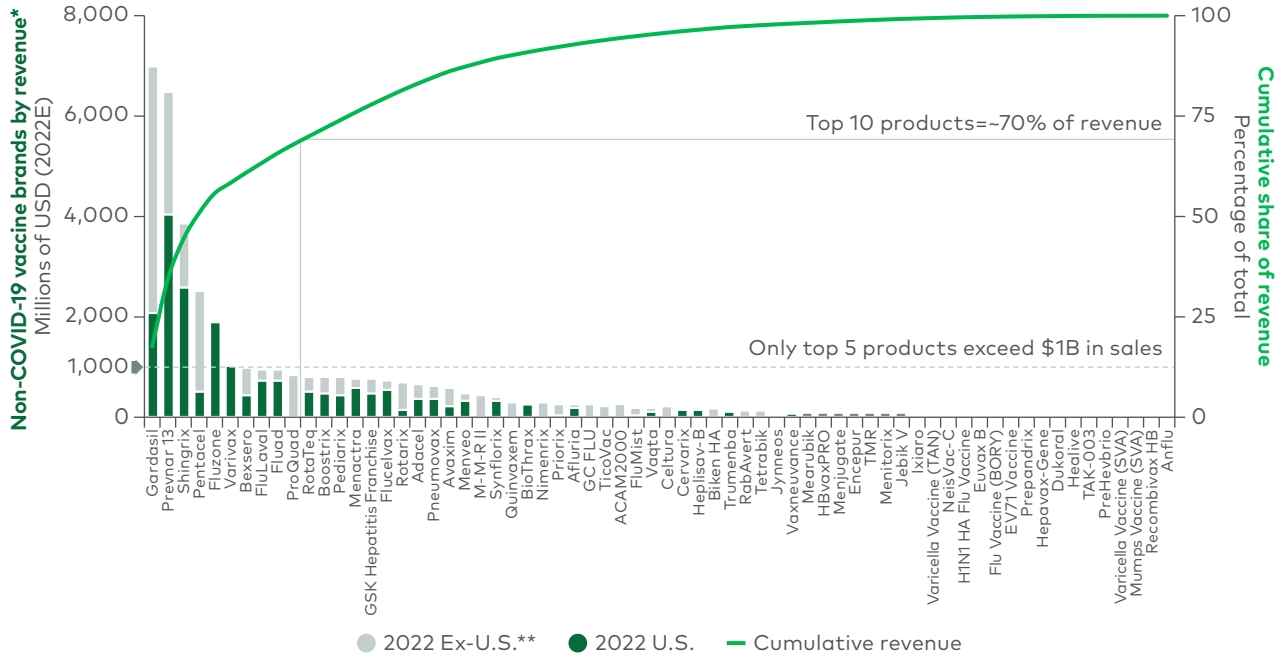
Governments and other payers may be unwilling to pay high prices for a widely distributed vaccine even if it is cost-effective. For example, in the U.S., the average noninfluenza vaccine costs approximately $110 per dose in the private sector. Most influenza vaccines are priced quite a bit lower, in the $20-$60 range. Even the most expensive vaccines, such as Gardasil, Prevnar and Bexsero, are priced at a few hundred dollars per dose. These prices are far lower than the cost of most novel branded prescription therapeutics.

Additionally, unlike with treatments for chronic diseases, patients may only receive a vaccine course once (e.g., a pediatric hep B vaccination requires three doses over six to 18 months), seasonally (e.g., for influenza) or even less frequently (e.g., a Td or Tdap vaccination every 10 years), which can further limit recurring revenue. To that end, many COVID-19 vaccine manufacturers have signaled that they will increase prices from about $20 per dose to $110-$130 per dose as they transition to the commercial market.

These pricing pressures are a major reason why only five non-COVID-19 vaccine brands exceeded $1 billion in estimated worldwide sales in 2022, accounting for approximately 55% of the market (see Figure 3). Parallel to lower revenues, lower pricing also reduces profit margins. This is especially critical for small and emerging biotechnology companies that may not be able to benefit from economies of scale.

Figure 3

Non-COVID-19 infectious disease vaccine revenue is concentrated in a few large brands, with limited blockbuster opportunities to date



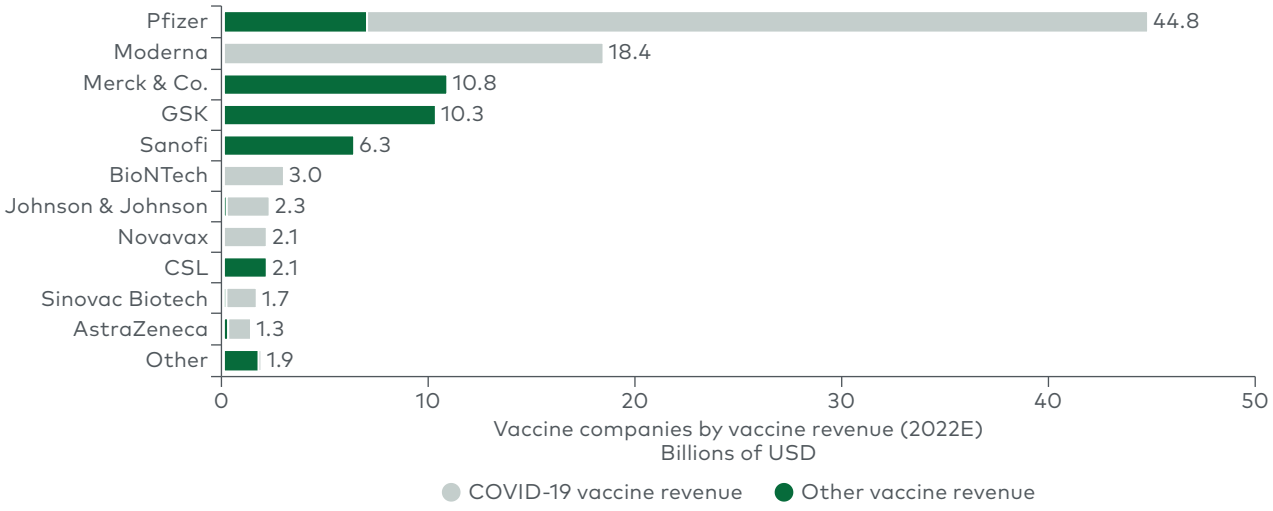
*May be nonexhaustive
**May include U.S. sales if U.S.-specific numbers not available
Source: EvaluatePharma; FDA; CDC; L.E.K. research and analysis

Entrenched players dominate the vaccine landscape

To mitigate these challenges, a company must possess certain characteristics. Access to capital and a strong balance sheet enable a company to make at-risk investments and accelerate the pathway to market. Strong clinical development and regulatory affairs teams use these investments to rapidly conduct trials and file for approvals. As mentioned above, manufacturing scale, flexible and diverse supply networks, and relationships with distributors enable a developer to react to unexpected market dynamics and provide alternative development and distribution pathways when supply chain challenges arise.

A diversified portfolio and pipeline can mitigate lower vaccine margins, and large, well-utilized manufacturing and supply chain infrastructure can provide economies of scale that reduce costs. Not surprisingly, only a handful of large pharmaceutical companies possess these characteristics and therefore dominate the non-COVID-19 vaccine space (see Figure 4). These companies also have entrenched relationships with key stakeholders that can make it even more difficult for newcomers to compete.

Figure 4
The vaccine space is dominated by a few big pharma companies with large-scale manufacturing and distribution capabilities as well as diversified portfolios with different therapeutics



Source: EvaluatePharma; L.E.K. research and analysis

Novel vaccine technologies have great potential, but questions remain

The COVID-19 pandemic stimulated an increase in innovative vaccine technologies. While mRNA may be the most popularly known, DNA and viruslike particles (VLPs) have advanced in recent years. These technologies have the potential to meet several unmet needs and have already begun to address some of the challenges and barriers to successfully entering the

vaccine market. For each of these novel technologies, however, there are questions that must be addressed before their long-term utility is proven (see Figure 5).

Figure 5
Nontraditional vaccine approaches may help address some of the challenges associated with developing a commercially successful vaccine

	Benefits/opportunities	Questions/challenges
mRNA Antigen-encoding RNA generally delivered in lipid nanoparticles	✓ Accelerated development timelines ✓ Easy to adjust to new strains or diseases ✓ Relatively simple manufacturing — does not require protein synthesis or purification	× May require complex cold storage from manufacturing to delivery × Potential safety concerns (e.g., myocarditis) × Unclear long-term durability
DNA Antigen-encoding DNA generally delivered by transfection	✓ Theoretically fast development timeline ✓ Safe manufacturing process ✓ More stable than mRNA, eliminating complexity from the supply chain	× Immunogenicity may vary with transfection method × No proven or approved products in humans
Virus-like particles Noninfectious particles resembling viruses in structure	✓ Induces a similar immune response to an infection and may be more durable ✓ Possible to target multiple epitopes ✓ Clinical, regulatory and commercial success (e.g., Gardasil)	× Likely slower development timelines than those of mRNA and DNA × Slightly more complex manufacturing × Few vaccines have been approved

Source: Tariq et al., Frontiers in Microbiology, 2022; Li et al., Signal Transduction and Targeted Therapy, 2022; Mohsen et al., CMI, 2022; L.E.K. research and analysis

- **mRNA:** mRNA accelerated development timelines for COVID-19 vaccines in part because it requires generating only the protein-coding nucleic acid (and lipid capsule) rather than the protein itself. This has potential to accelerate the timelines for developing novel vaccines and updating existing ones — as an example, updated protein-based COVID-19 vaccines may take up to six months to develop and manufacture, while updated mRNA vaccines may be ready in as little as 100 days. Despite their utility, some safety concerns remain (e.g., myocarditis) and the drug product itself has intensive cold-storage requirements. Additionally, the long-term durability and efficacy of mRNA vaccines compared with more traditional approaches remains an open question.
- **DNA:** DNA vaccines may be able to overcome some of the drawbacks associated with mRNA. Most importantly, DNA is substantially more stable than mRNA, reducing the cold-storage requirements and some manufacturing complexity. The benefits are also similar to mRNA when compared to traditional approaches — protein does not need to be synthesized, and both manufacturing and administration are thought to be safe. However,

immunogenicity varies with the transfection method and no intradermal vaccine has worked in humans, nor has any been approved to date.

- **VLPs:** VLPs are noninfectious particles that resemble viruses in structure but do not contain any genetic information, increasing safety even as they cause a similar immune response to an infection, theoretically increasing efficacy as well. These particles are manufactured to express relevant viral proteins on their surface with an implied ability to target multiple epitopes. This has potential to broaden coverage across strains and perhaps even improve durability. Although the manufacturing timeline may be more rapid than more traditional approaches, VLPs are likely to trail mRNA and DNA in development time. Though VLPs have seen clinical and regulatory success in certain vaccines, particularly Gardasil, there is substantial room for growth.

New or recent entrants to the vaccine market must carefully consider several important questions

Although COVID-19 has increased interest and investment in vaccine development, potential players need to carefully evaluate their ability to compete. Smaller vaccine developers should be realistic about their ability to scale and self-commercialize. Larger players intending to develop and commercialize novel vaccines should make sure they have the right capabilities at scale to win. The vaccine market is often winner takes all, so given the inherent difficulties of succeeding, there are several questions that a new or recent entrant must consider before pushing its chips into the center of the table:

- Which indications are attractive to enter based on commercial potential as well as development requirements?
- Do we have a differentiated vaccine/technology/capability uniquely positioned to address an unmet need in these attractive indications?
- What performance thresholds must be met to drive adoption, and what is the probability our vaccine/technology can meet them?
- Do we have the R&D, regulatory affairs, clinical management consultants, supply chain and commercial capabilities to compete and win?
- Are there opportunities to drive greater value via partnerships, mergers or other creative deal types?
- What is the ideal go-to-market strategy?

Though the infectious disease vaccine space is crowded by incumbents, there is a substantial amount of innovation spread across a long tail of smaller vaccine players. Since these new technologies could have the potential to address unmet patient needs and overcome many of the hurdles associated with vaccine development, they could provide the substrate for success that could be paired with the domain expertise, capital and scaled capabilities required to win. This will not be easy and may require creative deal structures and nontraditional funding sources, but it could offer an opportunity to address a key public need more profitably.

For more information, please contact lifesciences@lek.com.

References

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- S&P Global Market Intelligence
- Citeline Inc.
- WHO COVID-19 vaccine tracker and landscape
- CDC website
- Tariq et al., "Frontiers in Microbiology", 2022
- Li et al., "Signal Transduction and Targeted Therapy", 2022
- Mohsen et al., "CMI", 2022
- L.E.K. experience, research and analysis

Methodology

Figure 1

To highlight the volatility faced by vaccine companies, L.E.K. selected the following biotech companies: Moderna, Vaxcyte, Dynavax, Valneva, BioNTech, Novavax, Vaxart, Altimmune, Innovio, Icosavax, HOOKIPA, EuBiologics, VBI Vaccines, SAB Biotherapeutics, Vaccitech and Bavarian Nordic.

Each company's market cap on January 2, 2018, was obtained from S&P Capital IQ and set to 100. If a company was private on January 2, 2018, the market cap on the first trading day of the first month following availability on S&P was set to 100. On the first trading day of each subsequent month, the relative change of each company was calculated by the following formula: (current market cap / starting market cap) * 100. We then took a straight average of the relative values weighting each company equally. The same methodology was used to generate a relative value for the XBI exchange-traded funds.

Figure 3

We queried EvaluatePharma on March 3 for all available products labeled as vaccines to obtain worldwide and U.S. sales for 2022. Any product with an indication categorized as "COVID-19 prophylaxis" was excluded from further assessment. Ex-U.S. revenue was calculated by subtracting the value of U.S. sales from worldwide sales. Any updates to 2022 sales data after March 3, 2022, were not captured. Therefore, these values may include estimates.

Figure 4

We queried EvaluatePharma on March 3 for all available products labeled as vaccines to obtain worldwide sales for 2022. We then took the sum of each company's vaccine products for 2022 and broke out COVID-19 sales using the SUMIFS function. We obtained non-COVID-19 sales by subtracting this value from total company vaccine sales. Any updates to 2022 sales data after March 3, 2022, were not captured. Therefore, these values may include estimates.

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