A SHOT in the ARM

How science, engineering and supply chains converged to vaccinate the world.

BY YOSSI SHEFFI

When the COVID-19 pandemic struck in early 2020, in what ultimately became perhaps the greatest global supply chain disruption since World War II, employees began working from home, consumers were battling to hoard toilet paper (detailing the origins of this and other shortages) and companies were navigating the combined impacts of changing consumer demand, disrupted suppliers, fractured transportation links and new workplace regulations. At the same time, I began watching another story unfolding in the laboratories of universities and pharmaceutical companies. Biomedical scientists and engineers around the world began a race to save civilization from the virus by developing a vaccine. Those scientists and engineers seemed to face very long odds of success in any reasonable timeframe given both the very long gestation periods typically required to create just the candidate vaccines for testing and the low rate of subsequent approvals of tested vaccines.

Developing a safe and effective vaccine wasn't the end of the challenge; it was just a first step in what would become the greatest product launch in human history: mass-producing these vaccines, distributing them to vaccination sites around the world and getting billions of people to come and get vaccinated. Mass-producing the vaccine meant creating all the supply chains needed to manufacture all the ingredients and raw materials required for the vaccine, many of which had been niche laboratory chemicals. Getting to scale entailed overcoming shortages of materials and industrial capacity.

Doing this required bringing the full might of science, engineering, supply chain processes and government resources to combat a critical global problem. Each of these four realms of human endeavor faced, and largely overcame, serious obstacles in pursuit of the goal of preventing more death, disease and economic upheaval from COVID-19. Overall, the great race to vaccinate humanity holds many lessons about product development, manufacturing, creating new supply chains, distribution and customer adoption of highly innovative, revolutionary products.

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Vaccinating even 70% of the world's population of 7.8 billion would require nearly 11 billion doses of vaccine (assuming two shots per person, which is a common requirement of many of the leading vaccines). Moreover, the potential need for booster shots to address either natural declines in immunity or the emergence of variants of the SARS-CoV-2 virus brings a high likelihood of demand for additional billions of doses in the

Yossi Sheffi is the Elisha Gray II Professor of Engineering Systems and Director of the MIT Center for Transportation and Logistics. He is also the author of six award-winning books including A Shot in the Arm: How Science, Engineering, and Supply Chains Converged to Vaccinate the World, *from which this article is excerpted. He can be reached at sheffi@mit.edu.*

future. Although a number of leading vaccine producers were targeting volumes of billions of doses a year, the scale of the challenge of vaccinating the world as fast as possible meant a clear need for much higher global capacity. In the quest to vaccinate the world, companies sought partners, innovated new ways of building factories, digitalized operations and optimized production processes.

Finding a big buddy

While BioNTech had its mRNA vaccine technology, the small German biotech startup knew that getting to scale quickly would require access to significant resources. In March 2020, they chose to partner with Pfizer (the second-largest pharmaceutical company in the world) with whom they already had a 2018 agreement related to developing mRNA-based influenza vaccines. (Pfizer revenues in 2019 were almost 500 times that of BioNTech.) In announcing the partnership, Mikael Dolsten, chief scientific officer at Pfizer, said: "We believe that by pairing Pfizer's development, regulatory and commercial capabilities with BioNTech's mRNA vaccine technology and expertise as one of the industry leaders, we are reinforcing our commitment to do everything we can to combat this escalating pandemic, as quickly as possible."

Pfizer poured $2 billion of its own money into the aggressive project. "For this one, everything happened simultaneously," a person familiar with Pfizer's efforts told the Wall Street Journal. The vaccine's manufacturing and supply chain were created while the product was still under development. Mike McDermott, Pfizer's president of global supply, added: "My team spent $500 million, before we even got out of clinical trials. So, all completely at risk. We didn't know if we had a product that was going to work."

More partners = more production

Many of the vaccine makers sought partners in order to quickly access needed capacity and geographic diversity. "We're leaving no stone unturned in terms of partnerships," said Alex Gorsky, J&J's CEO. "One of the most important lessons of the pandemic is the power of collaboration." Paul Lefebvre, who heads the COVID-19 vaccine supply chain at Janssen Pharmaceuticals said: "In addition to establishing a capable manufacturing network, it's really important to have multiple manufacturing sites located in various regions to maintain the continuity of our supply chain." J&J's Stevens concluded: "Really, it is about, how do we think about partnerships? How do we think about leveraging sources of supply? But [it's] also really [about] continuously balancing our supply lines to serve the world in the most effective way."

Other vaccine makers also sought partners. For example, Moderna contracted with Lonza, a Swiss pharmaceutical contract manufacturer, to further increase the scale of production, especially in Europe. That contract manufacturer too had been preparing for rapid scaling. Two years earlier, Lonza invested in a shell-based strategy for building new factories. Instead of constructing purpose-built facilities for specific products after Lonza got a contract, the company designed and pre-built empty shell buildings that were pre-equipped with all the basic utilities and facilities (sterile water, steam, gas, data networks, etc.) needed for pharmaceutical manufacturing. Torsten Schmidt, leading the production facility in Switzerland, said: "The empty shells allow us to drop in the manufacturing technology that is needed for a particular drug or vaccine. This is important given that vaccines and drugs are becoming more diverse and a facility for one drug or vaccine cannot be easily used for another type of molecule."

Andre Goerke, Lonza's global lead for the Moderna project, said in an email to the American Chemical Society's Chemical & Engineering News: "Since we signed the agreement with Moderna in May this year [2020], the focus has been on getting four manufacturing kits up and running, each capable of producing an estimated 100 million doses of mRNA-1273 per year." Schmidt added, "In this pandemic situation, we are working around the clock to set up manufacturing in around eight months, compared to the two or more years it would usually take."

Accelerating the learning curve for production

Vaccine manufacturing operates at different scales as it progresses from lab to jab: research scale (the equivalent of a few doses for in vitro or in vivo animal studies), clinical trial scale (hundreds to tens of thousands of doses) and mass production (millions to billions of doses). At each stage, the vaccine maker's scientists learn something about the effectiveness and safety of the vaccine. Similarly, at each stage, the vaccine maker's production engineers learn something about the speed, yield and processing parameters of making the vaccine. Getting to scale quickly means being able to learn and apply lessons quickly, and that implies being able to make the best use of data.

Along those lines, to accelerate development and manufacturing at Moderna, Marcello Damiani, the company's chief digital and operational excellence officer, said: "We decided from the get-go to make it paperless." Moderna's all-digital strategy starts in the research phase. Researchers use a web platform for designing genetic sequences for new mRNA products, which enables direct production of research sequences in a fully automated central lab. Internal digital collaboration between scientists and engineers helps improve those genetic sequences for manufacturability and yield.

All of Moderna's equipment connects into its digital platform so that every step of the process collects data. "Between the small-scale research to the large-scale manufacturing, if you collect data from the different type of instruments, you are

learning, and that's the key piece," Damiani added. "Once you have the automation, the Internet of Things and the integration on the Cloud, you have data that's flowing, and you can start doing sophisticated analytics," he continued. "All this learning started at very small scales, and with this learning we had in place, we built our clinical manufacturing and GMP manufacturing." Damiani concluded by saying: "So, you see how we built the company, and I think the line between all this is data, data, data, because we collect the data to improve."

The quest for quantity: From setback to upsurge

In early fall 2020, Pfizer's chairman and chief executive Albert Bourla told employees: "Every ounce of our ability has been spent and nearly $2 billion put at risk." Initially, Pfizer had hoped to deliver 100 million doses by the end of 2020 and 1.3 billion doses in 2021. Despite the all-out effort, Pfizer faced serious challenges in production and supply chain operations, as scaling up the raw material supply chain took longer than expected. In November, the company realized it could not achieve its original production targets and cut the 2020 production forecast in half, to 50 million doses.

As Pfizer and BioNTech worked to overcome the obstacles to fulfilling their original forecasts, they also began pushing to vastly exceed those forecasts. They expanded their European manufacturing network from three partners to 13. BioNTech also recruited more manufacturing capacity from other larger pharmaceutical companies, such as Novartis and Sanofi. BioNTech reported capacity-boosting initiatives that included "the optimization of production processes, the recent initiation of production at BioNTech's Marburg, Germany facility, regulatory approval for six-dose vials and the expansion of [its] manufacturing and supplier network." Manufacturing engineers cut the batch production time nearly in half (from 110 days to about 60 days). Improvements in uniformity cut the waste on vial inspection lines from about 5% to about 1% to 2%.

Some of the efforts to boost production caused short-term delays in deliveries, such as when Pfizer renovated its Belgium facility in January to increase its capacity. During the upgrade, Pfizer suspended vaccine deliveries to Europe and Canada. European authorities threatened legal action because the delays forced them to suspend or reduce vaccinations. Charles Michel, president of the European Council, told radio station Europe 1: "We plan to make the pharmaceutical companies respect the contracts they have signed… by using the legal means at our disposal." In the end, the companies' efforts paid off, as Pfizer and BioNTech issued a steady stream of announcements during 2021, upping the 2021 delivery forecast to 2 billion doses in February, 2.5 billion in March and 3 billion in May.

The vaccine that came in from the cold

"Ensuring over a billion people globally have access to our potential vaccine is as critical as developing the vaccine itself," said Pfizer's CEO Bourla. Adding to the challenge of both the volume of shipments and the urgency of delivery was the need to properly handle the vials of vaccine while sending them to the far corners of the earth.

Whereas most vaccines require some refrigeration, the new mRNA vaccines require the most careful handling because of the delicate constitution of their lipid nanoparticles. Molecular biologist Phillip Sharp of MIT explained: "This is an oily particle with carbohydrate around it. So, it's a pain to keep it from fusing. It's just one big ball of oil if it's not taken care of. That's why all this shipping and freezing and thawing and everything is really very important."

Moderna's vaccine requires freezing between –50°C and –15°C (–58°F and 5°F), and Pfizer's requires ultra-low-temperature freezing between –80°C and –60°C (–112°F and –76°F). As a result, these vaccines require cold-chain handling: global distribution activities at very low and controlled temperatures.

The colder the temperature, the more challenging the cold-chain transportation and storage issues. In the case of the Pfizer vaccine's deep-freeze needs, very few facilities—only a handful of pharmaceutical distribution centers, hospitals and research laboratories—had the kinds of deep freezers needed. "I don't think we have all the cold storage that people think we have," commented James Bruno, president of the consulting firm Chemical and Pharmaceutical Solutions.

Helping shipmen ts keep their cool

As part of its parallel development strategy, Pfizer began setting up its downstream supply chain for the finished product in March 2020—at the same time as the kick-off of its Covid vaccine development. Pfizer said it developed a "just-in-time system, which will ship the frozen vials direct to the point of vaccination." That system included packaging for shipping, continuous monitoring of vaccine temperatures to ensure safety and a means to store the vaccine for up to a month at clinics, vaccination centers and distribution facilities that lacked deep freezers. These efforts used supply chain partners with respective expertise in cold-chain packaging and supply chain monitoring.

Pfizer worked with SoftBox, a multi-national British manufacturer of temperature-controlled packaging, to develop a reusable insulated thermal shipping box that holds 1,200 to 6,000 doses (at the six-dose-per-vial capacity). The box, measuring 17

× 17 × 22 inches, holds up to five small "pizza box" trays, each with 195 vials, in an inner payload sleeve box nestled deep in the heavily insulated outer box. On top of the precious cargo sits a "pod" with up to 50 pounds of dry ice at –109°F (-79°C). An insulated lid completes the cozy ensemble.

The result is a medium-sized, robust, 70- to 80-pound box (with side straps) that can be handled by any air or ground parcel delivery service. (Pfizer and SoftBox even designed the box to reduce the sublimation of the dry ice during flight, reducing the generation of potentially hazardous CO levels in air-freighters and significantly increasing the number of doses that air-freighters were permitted to safely carry.) As an added bonus, this thermal container can maintain ultra-cold temperatures for up to 10 days. Moreover, if needed, the recipient can replenish the dry ice every five days to extend storage in the box for up to 30 days. That enables facilities that lack the required freezers to temporarily store, distribute, and dispense the vaccine. Finally, when needed, the vaccine is thawed and can be kept in an ordinary refrigerator for up to five days before dilution and injection.

A view to a chill

To maintain 24/7 visibility onto shipments, Pfizer contracted with Controlant, a provider of real-time supply chain monitoring devices that go into shipping boxes. A small, battery-powered sensor tracks vaccine temperature, the opening of the box and its GPS location. Using a standard cellular data connection, the sensor sends the information in real time to Controlant's Cloud-based software, where customers can receive alerts and view the information. When the box is opened, red-green status lights show the shipment's temperature status, data connection status and battery status. "Controlant's reusable, real-time data loggers and visibility and analysis platform integrates with Pfizer's existing control tower technologies," said Tanya Alcorn, vice president of biopharma global supply chain at Pfizer, "to help manage temperature proactively, identify and react expeditiously to any events that can impact the supply chain, all while automating quality and logistics processes."

One tricky issue with the monitoring system occurred at the handoff when Pfizer delivered the doses to government distribution or vaccination centers. As the shipment left Pfizer's hands, Pfizer turned the monitoring off for legal liability and practicality reasons; once delivered, Pfizer had no control over the status of the shipment or the means to make the recipient take a corrective action. But recipients wanted the ability to monitor the boxes too, especially if they planned to use them for interim storage by refilling the dry ice. Fortunately, because the monitoring device was actually made and monitored by a third party, Controlant, all any recipient had to do was to sign up with the tracking company to restart monitoring and route the data and alerts to the recipient.

Getting ready to move 'em out

Pfizer bought large numbers of deep freezers to set up freezer farms to buffer and distribute the output of its production facilities in Michigan and Belgium. The company also built its own dry ice plant to make the freezing pods that keep the vaccines cold during transit. As of November 2020, Pfizer planned to have a fleet of 24 trucks to ferry shipments from Pfizer's facilities to local airports, where a combination of air charter and air freight companies such as FedEx, UPS and DHL could carry the vaccine anywhere in the world within a day or two. As the clinical results of the Phase 3 trials confirmed the efficacy of the Pfizer– BioNTech vaccine, Pfizer announced plans to move roughly 7.6 million doses per day.

Similarly, airfreight companies and facilities prepared for the vaccine distribution campaign. UPS, for example, built its own freezer farms and dry-ice production equipment at key air hubs. Airports invested in additional security and cold storage. Airlines conducted trial runs of vaccine deliveries to both debug systems and ensure the CO emissions from the dry ice remained within FAA-required limits. In coordination with Operation Warp Speed, FedEx and UPS divided the U.S. in half to improve delivery efficiencies. The efforts were intended to ensure fast, efficient and problem-free delivery of the vaccines once they were approved and started shipping.

The bigger picture of bigger demand

Overall, vaccine suppliers had to face and overcome a long list of challenges: Shortages began in the product development labs, moved into the ingredient supply chains and then hit the packaging ends of vaccine development and production processes. Shortages also hit capital equipment supply chains as pharmaceutical makers attempted to ramp up their capacity. As the adage goes, supply chains are only as strong as their weakest links. Successfully delivering large quantities of a new product depends on delivering all of the required quantities of every one of the raw materials, ingredients and all other parts in the bill of materials (BOM) of the final product, as well as all the plant equipment and machinery needed for manufacturing and delivering the product. Supply chains aren't about doing one thing well; they are about doing every one of many things well, because final products and customer satisfaction depend on every one of those many things for a complete, high-quality product delivered on time.