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Delivering 3 billion doses of Comirnaty in 2021

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Pfizer created a 'light-speed' approach to meet the challenge of vaccinating the world against COVID-19. It involved developing new strategies for all aspects of vaccine development, from sourcing materials and scaling up manufacturing to transportation and dosing.

In early 2020, it became clear that SARS-Cov2 presented a global health crisis. Although there had never been an mRNA product (vaccine or therapy) licensed in the world, we thought mRNA vaccines could offer a potential solution, with a key advantage being the rapid design-to-production timeline[1]. Moreover, an mRNA–lipid nanoparticle (mRNA-LNP) platform approach could enable rapid evaluation of vaccines against novel strains as they arise.

In hindsight, the speed to develop and manufacture Comirnaty was unprecedented. It took a mere 7 months to go from the first reported case of COVID-19 to initiation of the pivotal trial, and 11 months to Emergency Use Authorization in the United States. In contrast, the time to develop an Ebola vaccine in response to the 2014 West Africa outbreak was 16 months to get to the pivotal trial and 70 months to approval[2]. Looking farther back in history, it took decades to go from pathogen identification to first approval for meningitis, whooping cough, measles and hepatitis vaccines[3]. The polio vaccines, while highly successful, took years to develop, test, manufacture and administer globally, starting from 1952; it was licensed in 1955 in the United States and distributed well into the 1960s. Whereas it takes many years to develop a vaccine and gain approval, largely because of the time it takes to conduct clinical trials, fully developing the large-scale manufacturing process intended for commercial production has always been a multiyear effort because of the science and engineering required to develop a robust process and the regulatory requirements for approval.

To speed manufacturing process development and scale up without sacrificing quality, Pfizer and BioNTech mobilized talent and developed a light-speed plan, working on critical aspects of the project in parallel rather than sequentially. Pfizer and BioNTech advanced Comirnaty from research to product, gaining authorization in December 2020 and manufacturing 3 billion doses by the end of 2021. By February 2022, our COVID-19 vaccine had been approved for distribution in 170 countries and territories (Fig. 1).

In terms of speed and scale, the rapid development of Comirnaty may be the largest and fastest campaign of vaccine development and implementation ever attempted. Achieving this goal was not without challenges. In the following sections, we will describe our overall strategy to speed up the timelines and discuss several specific challenges in often underappreciated focus areas.

The strategy

Within the Pfizer Biotherapeutics Pharmaceutical Sciences and Global Supply organizations, we initiated parallel development of four COVID-19 vaccine candidates involving four separate work streams for plasmids, mRNA and drug product, as well as analytics and production facility planning (for example, process scale-up and eventual validation) while simultaneously processing initial clinical supplies. We reviewed our ongoing efforts across our facilities and portfolio and reassigned hundreds of colleagues to work on the mRNA-LNP program. To further increase the pace of development and manufacturing, we recruited, hired and trained hundreds of new colleagues to focus on mRNA-LNP process and product development and manufacture, in a manner that was inclusive, safe, focused and ultimately successful. Recruiting colleagues with specific expertise in mRNA or LNP development was challenging, and therefore we sought candidates who were bright and agile and could be trained quickly to contribute to this substantial effort, as well as backfill roles for colleagues who were reassigned to work on the vaccine candidate.

The final sterile vaccine lot comprises components and intermediates produced in several multistep processes: the starting DNA template manufactured via *Escherichia coli* fermentation from a well-characterized starting cell bank, the mRNA intermediate produced by in vitro transcription (IVT) from the DNA template, specialized lipids that form the nanoparticle, and the unique combination of the mRNA and lipids, followed by sterile filling and freezing to produce the final vaccine vials[4].

Whereas several of these processes may be common to other vaccines (*E. coli* fermentation and aseptic filling, for example), others had never been run at a scale suitable for a mass vaccination campaign. The IVT reaction and LNP production had been established at lab scale as well as pilot clinical scale, but not with the capacity to sustainably generate millions of doses per month. Furthermore, while the capacity for drug product stored at ultra-low temperatures had been used for small batches of gene therapy candidates, the scale to manufacture, store and ship a large-scale vaccine was unprecedented.

Challenge 1: securing critical resources to reduce supply chain uncertainty

Since mRNA vaccines are an emerging technology, the manufacturing equipment, production facilities and raw materials were not available at the start of the pandemic at the scale needed. Pfizer invested early and coordinated across a broad internal and external network to design and procure large-scale novel processing equipment (mRNA-LNP fabrication equipment, tangential-flow filtration skids, and custom designed reactors), reassigned existing facilities (aseptic manufacturing facilities, quality control labs, development facilities), and created new work processes and facilities (dry ice production capable of tens of tons per day). Establishing a path toward scaled-up vaccine manufacture while continuing to manufacture and deliver critical therapeutics was challenging and required agility across our manufacturing facilities and testing labs. The

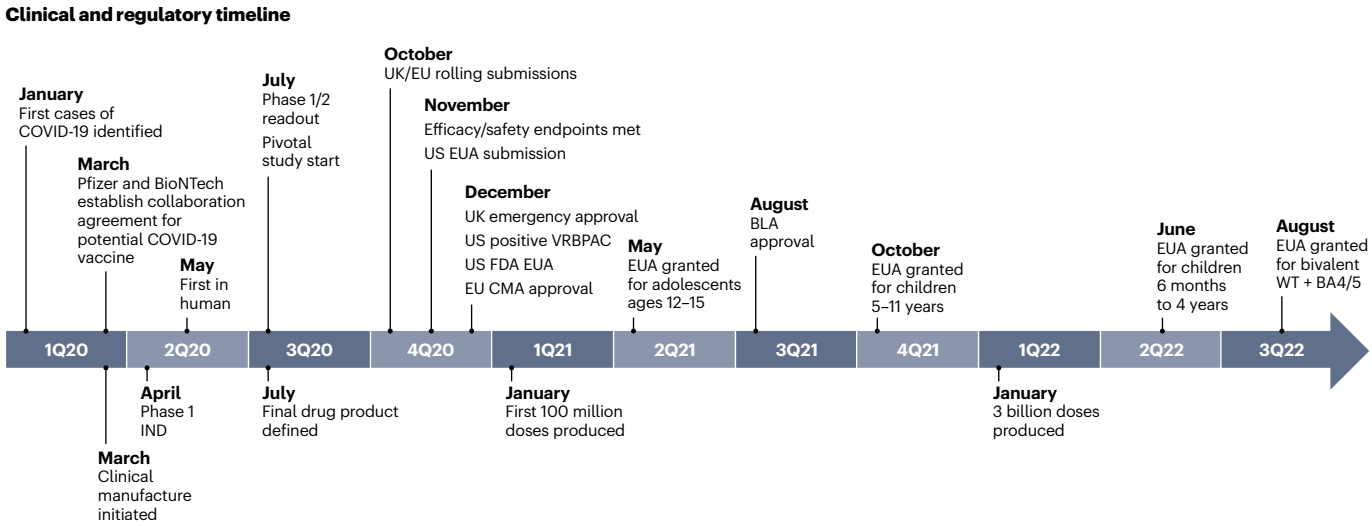


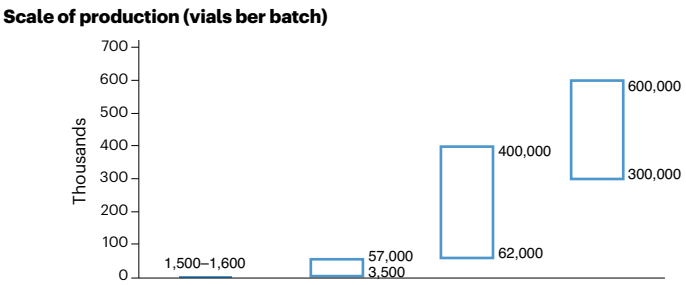
Fig. 1 | Timelines for Comirnaty development. Top line: clinical and regulatory timeline. Bottom line: development and manufacturing timeline. IND, Investigational New Drug; EUA, Emergency Use Authorization; VRBPAC, Vaccines and Related Biological Products Advisory Committee; FDA, Food and Drug Administration; CMA, Conditional Marketing Authorisation; BLA, Biologics License Application.

company committed up to $2 billion of at-risk investment for new types of equipment such as large-scale mRNA-LNP mixers based largely on bench-scale prototype models and processes. We created 'freezer farms' at multiple manufacturing and distribution sites where we installed thousands of deep freezers for mRNA-LNP vaccine drug product storage. We repurposed a pilot facility in Chesterfield, Missouri to produce the plasmid DNA template. We assigned a new flexible manufacturing facility in Andover, Massachusetts for mRNA drug substance production, and existing large-scale drug product facilities in Puurs, Belgium and Kalamazoo, Michigan for creation of the mRNA-LNPs, aseptic drug product manufacture, labeling, packaging and storage of the finished product. The ability to deploy and redeploy Pfizer's vast network of manufacturing and laboratories, existing as a result of previous investment in facilities and technology, was critical to our success.

We formed numerous industry partnerships with vendors, with many of whom we had pre-existing relationships, to secure materials and ordered large amounts of enzymes, lipids, and other supplies, at risk before receipt of clinical data or strategic production-focused decisions. This was necessary for ensuring consistent supply and quality of critical reagents and components, as we recognized that control of raw material supply and quality would be vital to our success. Managing raw materials posed several challenges. Supply chain interruptions impacted the pharmaceutical industry, and component lead times became extended from weeks to months (vials, stoppers, manifolds, filters and processing vessels, for example). Working with vendors as well as our internal network of manufacturing sites, we prioritized the need for Comirnaty production while not impairing ongoing production of licensed therapeutics. Managing critical raw materials and components drove the need for increased collaboration across our network of manufacturing and development sites to ensure sustained manufacturing.

We established productive relationships with vendors of specialty chemicals and worked with them to ensure scale-up and increased production without compromising the quality of the raw material (nucleotides, lipids, IVT-related enzymes). For several raw materials, and in consideration of the scale of production, we engaged and qualified multiple vendors to ensure adequate supplies as well as guard against supply chain interruptions and potential concerns regarding quality. For selected raw materials — custom lipids, for example — we developed internal manufacturing capabilities to support clinical production, as well as more rapidly enable scale-up and production at third-party specialty chemical vendors. To assess the quality of new raw material suppliers, we established lab-scale fabrication processes so that small-scale batches could be produced with new raw materials to assess the quality and stability of the resultant mRNA-LNPs; this provided us with confidence in the raw material and vendor across our manufacturing network. Procuring, testing, approving and tracking the approximately 280 unique components from 86 suppliers in 19 countries required experience, well-trained scientists and business experts who worked around the clock to assure all materials were in place, on time.

Pfizer invested in new analytical technology required for characterizing and quality control testing of a mRNA-LNP vaccine across a global network of labs in the United States and European Union. This included using advanced biochemical, biophysical and biological assays, such as dynamic light scattering, sequencing, and cell-based flow cytometry, in Good Manufacturing Practice laboratories around the entire Pfizer and BioNTech network. Further, we developed and validated methods to assess the quality of raw materials and each process intermediate (plasmid, mRNA, mRNA-LNP) to ensure consistency across batches and across the network of manufacturing sites. Since initial supplies were produced in Chesterfield (plasmid), Andover (mRNA) Puurs and Kalamazoo (finished product), we needed to ensure consistency not only between these manufacturing sites but at a growing number of other Pfizer, BioNTech and contract manufacturing sites and testing labs.



Process step	Phase 1	Phase 3/pivotal	Initial launch	2021 scale-up
Plasmid	PCR	PCR	Plasmid DNA	Plasmid DNA
mRNA DS	1 g	1–5 g	10 g	250 g–1 kg
DP (volume)			125 L	1,600 L

Fig. 2 | COVID-19 vaccine production scale. The scale of plasmid, mRNA drug substance (DS) and drug product (DP) production increased up to 1,000-fold.

The current manufacturing network spans 20 facilities across 4 continents, including many contract manufacturing partners. The expansion of our manufacturing and supplier network and continued investment in our analytics capabilities have enabled us to increase our overall capacity as well as realize a 50% reduction, since the initial product authorization, in the manufacturing and release time from DNA template start to completion of filling and testing of final drug product vials.

Challenge 2: ensuring high quality of the vaccine made at different scales and sites

The journey to a final batch, known as a "lot" of 300,000–600,000 vials of final vaccine, requires that operations be performed at several facilities with sophisticated equipment and highly trained personnel. The vaccine is made and tested in separate stages, starting with the DNA template, followed by the mRNA and finally the mRNA encapsulated in an LNP sterile filtered into the glass vials to be distributed. To ensure that each lot is of consistent quality, regardless of where it was manufactured and tested, an understanding of what is important about the product is essential. This foundational step involves a vaccine's critical quality attributes (CQAs) — those properties that assure safety and efficacy[5]. These CQAs are tested many times during the production of a lot and subject to multiple levels of process controls that are documented in production records, reviewed by quality assurance personnel, and defined in the regulatory authorization or license.

The CQAs of mRNA vaccines relate to the identity and quality of the DNA template and the mRNA, the quality of the lipid nanoparticle, and the ability of the mRNA to consistently be translated into spike protein. Each lot of mRNA-LNP must meet predetermined criteria in over 40 separate tests for product release. Each analytical method had to be developed for a unique CQA, as well as specific process steps, to demonstrate control and consistency of manufacture. For a quality control lab to be qualified to perform product testing, all equipment, methods and data analyses must be proven to be correct, and data must be bridged across labs to ensure consistent results. In addition, many batches of DNA template, RNA and final vaccine are put through controlled stability studies, designed to test these 40+ attributes at multiple time points over storage of the vaccine, to define acceptable expiry dating. This was a particular challenge as real-time stability data were generated on a just-in-time basis, and the Pfizer team needed to manage product expiry periods on the basis of available data and regulatory authorization. Because of the number of labs and manufacturing facilities involved, there were over 50 separate stability studies set up over the first year of COVID-19 vaccine manufacturing alone.

We developed scaled-up processes for plasmid DNA and mRNA to enable late-stage clinical supplies while also planning, in parallel, large-scale production in an effort to meet the needs of the global population. In addition, we both scaled up as well as scaled out the small-scale LNP fabrication process to ensure adequate drug product while reducing the risk of comparability concerns across production scales. For example, scale-up of the mRNA IVT process from lab scale (500 mL) to production scale (40 L and 128 L) required a series of engineering designs to ensure consistent scale-up as well as rigorous in-process controls and tests to establish that the scaled-up process is controlled and represents the small-scale process (Fig. 2). These large batch sizes (up to 600,000 vials per batch) are further amplified by the use of multi-use vials, resulting in production of up to 3.6 million doses per batch. Consistency in the process and in the quality of the mRNA is essential to demonstrate comparability, as well as providing confidence that the commercial-scale manufacture delivers product that is consistent with that assessed during the clinical trials. Similarly, scale-up and scale-out of the LNP process was particularly challenging as we did not wish to increase the internal dimensions of the device that creates the mRNA-LNP (referred to as the T-mixer or impinging jet mixer). Scaling out allowed us create the LNPs using a consistent T-mixer geometry regardless of scale, thus minimizing the risk of scale-driven changes in LNP characteristics. To enable greater production, up to eight sets of pumps and T-mixers were used on a single manufacturing line, with a central controller, to ensure that the quality of the LNPs at large scale was comparable to that of smaller, early clinical-scale LNPs.

The initial Emergency Use Authorization authorized manufacturing at five locations: a single node for the DNA plasmid (Chesterfield, Missouri), two nodes for mRNA drug substance (Andover, Massachusetts and Mainz and Rentschler, Germany) and four nodes for LNP manufacturing (two BioNTech contract manufacturing organizations; Kalamazoo, Michigan; and Puurs, Belgium). Quality control testing was supported by central multipurpose labs in Chesterfield and Andover, as well as the local labs supporting each facility. COVID-19 vaccine is now manufactured at and tested at 20 locations across the Pfizer and BioNTech network (Fig. 3).

Each change, along with introduction of new suppliers or scale-up exercises, results in a body of data and documents that must be submitted to all countries that authorized or approved the vaccine, requiring hundreds of colleagues at any one time working on regulatory documentation authoring and review, as well as responding to questions from regulatory bodies. Designing, implementing and approving the changes required to ensure continued vaccine manufacturing or testing remains an enormous life cycle management effort today. By leveraging hundreds of experienced colleagues across our global network, we were able to manage these changes and satisfy regulatory expectations, as well as meet the demand for millions of vials without compromising manufacture and delivery timelines.

Whereas all of these process — scale up or scale out, testing, validation, comparability and transfers — are part of manufacturing any quality vaccine, the magnitude, scale and speed at which these were implemented was unprecedented. Engagement and collaboration with the global regulatory authorities was remarkable as we shared a common goal of searching for a vaccine-based solution to the COVID-19 pandemic. There was collaboration, overnight and holiday discussions, and expedited method transfers to global labs. Scientists, engineers,

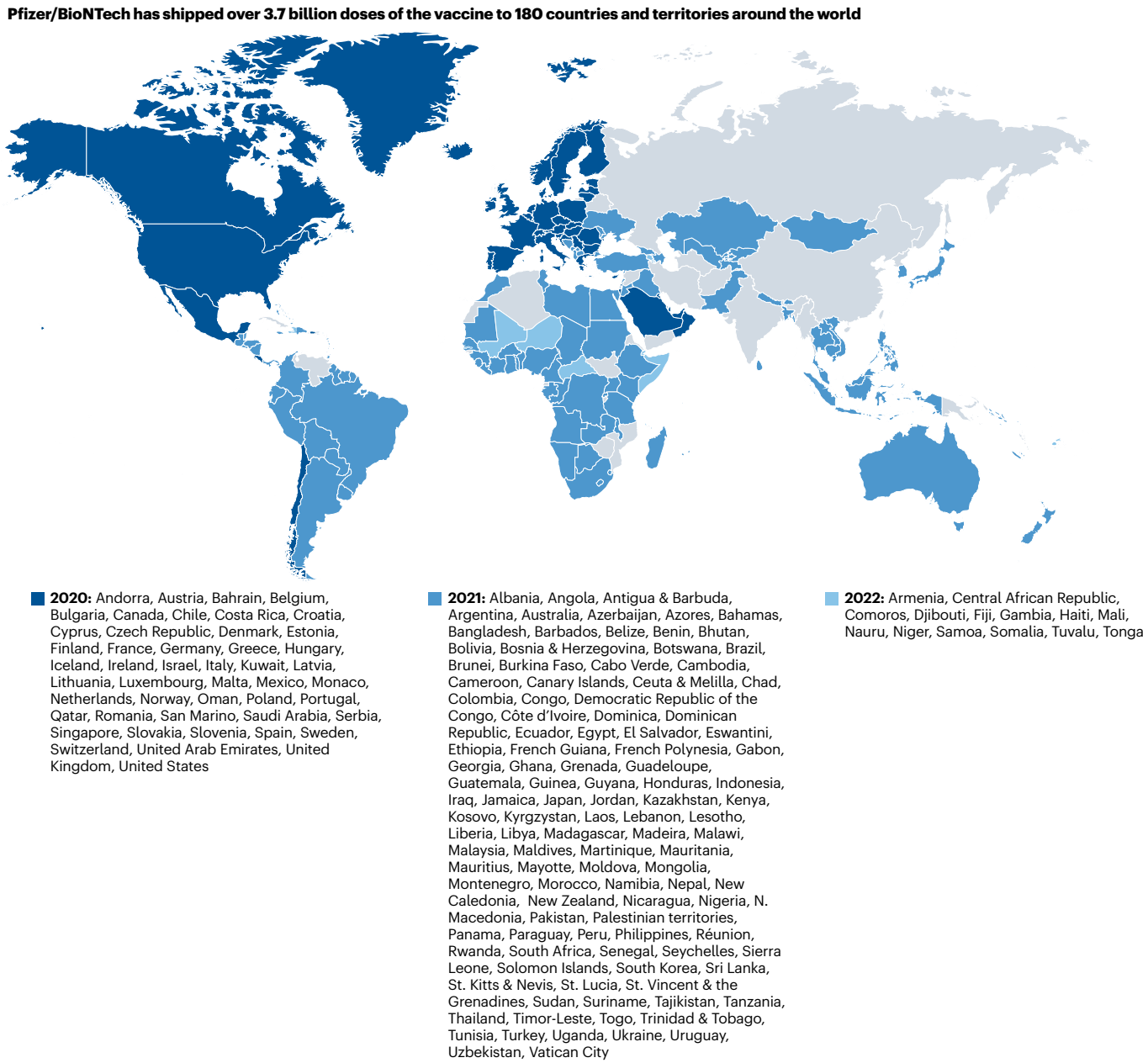


Fig. 3 | Global distribution of Comirnaty. Through 2022, Pfizer has globally distributed over 3.7 billion doses to 180 countries and territories.

regulatory colleagues and staff in regulatory agencies worked seven days a week to expedite submissions and review to ensure no day was lost while simultaneously ensuring that the quality of the product and the dossiers met the rigorous expectations both within the company as well as within the global regulatory community. To date, the Pfizer-BioNTech vaccine, and its expansive manufacturing and testing network, has been submitted and authorized or approved by more than 170 countries and territories.

Challenge 3: designing dose forms for convenience

The design of the final vaccine drug product vial was critical to maximize our facility output and rapidly scale up the number of doses per batch, thereby ensuring equitable vaccine distribution on a global scale. Designing the product as a six-dose vial and using low dead-volume components (syringes and needles) enabled us to produce 3 billion doses in 2021 without wasting doses left in the vial. A batch of 600,000 vials, for example, could deliver up to 3.6 million doses based on the six-dose vial design. Further, using a relatively small 2-mL vial enabled us to maximize the capacity of our ultra-low-temperature freezers as well as efficiently pack shipping containers and reduce the storage footprint at local pharmacies and hospitals. This yield of doses enabled us to increase our productivity as well as enable distribution of a substantial number of doses to low- and middle-income countries via the COVAX initiative and the US government (Fig. 3).

Fig. 4 | Pfizer global supply network map. Pfizer leveraged a global network of manufacturing sites to deliver Comirnaty.

The initial adult dosage form was a six-dose vial to deliver 30 µg per dose. This dose form, however, required dilution before use, which is inconvenient. After launch, we modified the composition of the formulation and reduced the concentration of the mRNA-LNP. Developing the new formulation enabled easy dose preparation and storage at the receiving pharmacy or clinic. By making these changes, we eliminated the dilution step as well as enabled 10 weeks of refrigerated storage after the vials are thawed, increasing flexibility at the pharmacy while retaining the efficient six-dose vial.

Challenge 4: transporting vaccine to people around the world

mRNA vaccines are intrinsically unstable, and while they can be stored at −70 °C to −80 °C for extended periods, transporting them around the world presented a major challenge.

We had to demonstrate that our vials and stoppers could withstand shipping and storage temperatures as low as −96 °C to support global distribution at a scale that we had never done before. This required careful selection and pairing of components as well as qualification of the stoppering and capping processes to ensure container-closure integrity at very low temperatures. Stability studies, mimicking temperature cycling, showed that the vials could be stored in ultra-low-temperature freezers and in refrigerators once thawed. Multiple batches from multiple sites were tested to provide confidence in the robustness of the product and its storage.

For global distribution, Pfizer invented a pallet shipper that uses dry ice to keep the temperature at an appropriate range. In addition, each shipper is equipped with GPS tracking to monitor its location, a thermometer to monitor its temperature, and a light meter to monitor whether the box has been opened. This tracking system was used to track each shipment across the globe to ensure that the product is handled properly and not mishandled during shipment or receipt. In addition to ensuring the quality of the drug product during shipping, the shipper boxes were further optimized to serve as short-term freezers at pharmacy locations where ultra-low-temperature freezers were not available. By reloading the shippers with dry ice, a local pharmacist could use the shippers to safely store the vials as patients arrived to be vaccinated, reducing the burden on pharmacies or dosing centers to offer ultra-low-temperature storage.

Pfizer delivered 1 billion doses of Comirnaty to low- and middle-income countries in 2021 via a number of supply pathways (governments, supranational organizations such as COVAX and government and humanitarian donations). These shipments used the same shipper and controls as those delivered in the United States, Europe and elsewhere. Pfizer also conducted extensive shipping simulation studies under various conditions (temperatures, modes of transport) to ensure that even when vaccine leaves Pfizer distribution networks, transportation can be performed safely to enable last-mile distribution and ensure the vaccine can safely reach all communities. In addition to shipping via commercial routes, Pfizer used its ongoing relationship with Zipline to deliver Comirnaty to hard-to-access communities via drone.

Lessons learned and future perspectives

Long-term Pfizer investment in a strong pharmaceutical science and manufacturing network provided a sound foundation for the development of the COVID-19 vaccine product, including a robust manufacturing process and analytics. A broad network of Pfizer sites and previous investments in capacity and capability prepared us to rapidly pivot to plasmid, mRNA and drug product development, manufacture and analysis. Figure 4 presents a global view of the Pfizer manufacturing network that supports the manufacture and distribution of

Comirnaty. Large-scale Current Good Manufacturing Practice manufacturing capacity and know-how provided us with in-house facilities and experience to quickly scale up production simultaneously across sites. Mobilization of highly trained staff onto this urgent project, at risk, from engineering to procurement to development, was critical as we sought to keep our colleagues and their families safe during the COVID-19 pandemic.

The company made a large investment in process and product development and production before any clinical data became available, even though it was a substantial risk. Cutting red tape was also a key enabler: we sought to reduce roadblocks (that is, investment decisions), streamline decision making, and enable colleagues to make decisions based on data and risk assessment.

The mRNA-LNP process is effective, scalable and agile. By identifying a variant of concern and obtaining a sequence of the new spike protein, we can modify the sequence of the plasmid DNA and move to production quickly to make clinical supplies as well as commercial-scale plasmid, mRNA and mRNA-LNP drug product. The speed to transition, culminating in a regulatory submission, is fast. Our team has a goal of responding to new variants within 100 days, which was achieved with the authorization of the bivalent vaccine in August 2022.

In spite of this progress, challenges remain in mRNA-LNP vaccine manufacturing. Life-cycle management, including improvements in processes and products, is a resource-heavy activity involving management and updates of global regulatory licenses. Continued streamlining of regulatory requirements and collaboration with regulators is key to enable continued improvements to product capability and capacity and to respond to future pandemics. Creating a convenient refrigerator-stable mRNA-LNP vaccine is a priority to continue to provide global access to as many patients as possible.

Finally, shortening end-to-end mRNA production timelines to support the changing public health needs such as boosters, strain changes and variants of concerns will be critical to enable timely responses to new variants that may challenge public health.

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Competing interests

The authors are employees of Pfizer, Inc. and have been engaged in the development and manufacture of Comirnaty.