MODERNATM IS CREATING a new category of transformative medicines based on messenger RNA (mRNA) to improve the lives of patients. We designed our strategy and operations to realize the full potential value and impact of mRNA over a long time horizon across a broad array of human diseases. We built a platform technology to control the quality of the entire process, from raw materials to end product and to speed the time to market. We also focused on forward investments in scalable infrastructure and capabilities. We believe manufacturing plays a critical role in our value chain and ability to develop a new category of medicines.

After receiving our first positive clinical data in our infectious disease portfolio, we began building a dedicated in-house manufacturing facility in Norwood, MA, in expectation of significant ongoing pipeline expansion and the long lead time required to create appropriate infrastructure. Facility construction began in October 2016 and was fully operational by July 2018. The site comprises 200,000 sf (Figure 1) and supplies our Research Engine, Investigational New Drug (IND)-enabling toxicology studies, early clinical, and late-stage clinical trials. The facility can also accommodate specific commercial launch activities.

Our Norwood facility has been designed with a high level of automation and digital integration of manufacturing records and data. State-of-the-art digital management systems handle material resourcing, manufacturing execution, laboratory information, asset control, and documentation. These systems ensure the digital integration of our manufacturing, product testing and release, and regulatory filings.

Create and Make: Technical Development and Manufacturing Engines

To support our broad pipeline of products spanning multiple therapeutic areas and modalities, the technology underpinning our product manufacturing is essential to our success. We have invested heavily in our platform technology to enable the breadth and depth of our pipeline, preparing us to meet future needs and requirements as our programs enter later phases of development and commercialization (Figure 2).

At Norwood, our process development ("create") and manufacturing ("make") capabilities are co-located which enables us to move more quickly from idea to implementation. We are expanding the Technical Development footprint at Norwood by adding an additional 220,000 sf. centralized digital integration of key systems and data streams support a rapid and effective continuous improvement feedback loop between development and manufacturing.

Figure 1: The Norwood manufacturing facility is a 200,000 sq ft facility with >300-person capacity.

Figure 2: The evolution of Moderna manufacturing, 2011–2019. Norwood enables improved quality, speed, scale, and cost by internalizing the entire process, from raw materials to shipping to clinical sites.

**Abbreviations:** FFF, formulation, fill, finish; LNP, lipid nanoparticle; QC, quality control.
At Norwood, our process development ("create") and manufacturing ("make") capabilities are co-located so we can move quickly from idea to implementation.

**CREATE**

**Technical Development**

Our Platform Research team’s frequent and significant breakthroughs in mRNA science enable Moderna to develop therapies to serve a widening patient population. Close collaboration between our Platform Research and Technical Development teams facilitate rapid and seamless clinical translation of scientific breakthroughs. Technical Development encompasses the design and optimization of robust and consistent manufacturing processes, product characterization, fit-for-purpose formulations, and product presentations. Our novel hardware platforms’ significant automation and robotics, coupled with the flexibility of our custom in-house digital development system permit thousands of experiments and process parameters across our projects. These capabilities support our drug product pharmaceutical readiness.

Our technical manufacturing advances over the last few years have enabled internalization of new key capabilities (e.g., DNA plasmids and small molecules). In parallel, we have refined existing processes, resulting in increased manufacturing scale and more robust stability of our mRNA and drug product. These improvements allow us significant control over our supply chain, resulting in larger production yields and longer shelf life of our products. Furthermore, formulation development advancements have added new drug product images including lyophilization, giving us a path from frozen to refrigerated storage conditions.

**MAKE (ENGINE 1)**

**Preclinical**

High-throughput automation and custom engineered equipment allow us to produce high-quality mRNA and formulated constructs within a few weeks from order to delivery: our proprietary platform is capable of producing up to 1,000 lots of mRNA sequences and formulations per month with a turnaround time of a few weeks from sequence to final product. The typical scale of mRNA manufactured by this team is 1–1,000 mg. Since 2014, we have produced >23,500 batches of research-grade mRNA. Researchers in the Moderna ecosystem can order constructs through an integrated digital portal that tracks materials from start of the manufacturing process through delivery in less than 30 days. Multiple integrated algorithms using artificial intelligence and machine learning optimize manufacturability, reduce failures, and increase quality of mRNA sequences.

Since 2014, we have produced more than 23,500 batches of research-grade mRNA.
**MAKE (ENGINE 2)**

**Personalized Vaccine Unit**

Due to the specialized nature of personalized medicine, in which a batch is specifically designed and manufactured for a single patient, Personalized Vaccine Unit (PVU) manufacturing has unique requirements. Our first product is the Personalized Cancer Vaccine (PCV), for which we digitally integrate patient-specific data from sequencing tumor samples to automatically designing PCVs for patients. We have developed proprietary bioinformatics design algorithms linked to an automated manufacturing process for rapid production of formulated mRNA. Turnaround time is typically a few weeks. We have operationalized PCV manufacturing at Norwood to meet our Phase 1 and 2 pipeline supply needs by using single-use systems with fast “needle-to-needle” turnaround times (Figure 4).

Unlike traditional process development, where the product is scaled up in quantity for later phases of development and commercialization, each PCV batch is manufactured for a single patient and thus scaled-out (in parallel) with extensive use of automation and robotics for the larger numbers of patients involved in later phases of development and commercialization. We have shown consistent quality in our production of >90 patient batches, each with unique mRNA sequences, using the same process and achieving consistent quality attributes.

**MAKE (ENGINE 3)**

**Clinical**

We are supplying clinical trial materials for human studies. Prior to Norwood, we operationalized two Current Good Manufacturing Practice (cGMP) suites in Cambridge, MA. These suites supported phase I clinical trials by supplying mRNA and formulated lipid nanoparticles (LNPs). This manufacturing experience informed process scale and user requirement specifications for the design of the Norwood facility. Our Norwood facility meets cGMP standards and has fully integrated end-to-end capability from production of critical raw materials (e.g., plasmid), mRNA, formulated LNP drug product, sterile filling, and labeling and packing. All manufacturing areas are supported by a digital backbone that captures process variables in real-time electronic batch records and thus facilitates rapid process changes. Moderna also has external manufacturing at well-established CMOs for redundancy. This planned flexibility and capacity for scaling cGMP manufacturing has enabled our broad pipeline of 24 development candidates.

We have developed deep expertise executing clinical batches for our Core Modalities in infectious disease and systemic secreted and cell surface therapeutics—allowing us to move faster, with higher quality, and at lower cost. The flexibility of Norwood, along with the integration of technical development and manufacturing, means we can quickly pivot and support exploratory programs that require integration of new capabilities.

**Anticipating the Future**

We have produced >100 clinical batches in Norwood since July 2018. Having all the engines under one roof has accelerated our learning.

We are harnessing the power of the platform—its digital integration and our end-to-end manufacturing capabilities—and applying the learnings to future batches with an end result of rapidly improving our quality, speed, scale, and cost.

**At the upcoming Norwood Manufacturing and Digital Day on March 4, 2020,** we will present real case studies that demonstrate this Accelerated Manufacturing for Patients, digital integration, and the benefits of our platform approach.