Smart Vaccine Manufacturing Using Novel Biotechnology Platforms: A Study During COVID-19

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Healthcare experts have come to a consensus that effective and safe vaccines are necessary to control the rapid spread of the ongoing COVID-19 pandemic across the globe. Since the traditional vaccine development and manufacturing approaches were unable to meet the rapidly growing COVID-19 vaccine demand, biopharmaceutical firms had to devise novel and smart techniques to boost the development, production, and distribution of COVID-19 vaccines in a large scale with lightning speed. This triggered their transition to smart vaccine manufacturing approaches using novel viral vector and nucleic acid biotechnology platforms. This paper tries to explore this rationality of the biopharmaceutical industry by comparing the traditional and the novel biotechnology platform-based vaccine manufacturing techniques and reviewing the COVID-19 vaccine manufacturing scenarios. To highlight the "smart" characteristics of the novel platform-based COVID-19 vaccine products and to make an effective comparison with the traditional products, a well-established product classification framework is used as a reference. Finally, the study concludes by presenting the future possibility of incorporating smart manufacturing paradigms with the novel platform-based manufacturing process. It is hoped that this study would serve as an asset for the biopharmaceutical firms to appropriately streamline their strategies, resources, and goals to meet the global vaccine requirements. [DOI: 10.1115/1.4053273]

Keywords: product platforms, vaccines, smart manufacturing, vaccine manufacturing, Covid-19, cybermanufacturing, data-driven engineering, information management, manufacturing automation

1 Introduction

A vaccine is usually made from a very small amount of dead or weak germs such as bacteria and viruses that cause diseases. Vaccines help the body fight against diseases effectively and quickly by stimulating the body's natural immune response so that the risk of getting the disease from the actual pathogen is reduced. The global outbreak of the COVID-19 pandemic has triggered rapid advancement and application in the field of biotechnology, especially vaccine manufacturing. This sector is undergoing tremendous transformation, and significant investments have been made to develop vaccines at "lightning speed" [1,2].

To meet the growing demand for vaccines during the COVID-19 pandemic, biopharmaceutical firms have shifted their focus from the traditional vaccine manufacturing techniques using attenuated or inactivated viruses to the novel "biotechnology platform"-based techniques for vaccine manufacturing. Vaccines developed using these novel platforms share a common set of ingredients and manufacturing processes that have been independently developed and tested by the biotechnology industry. According to the World Health Organization (WHO) estimates, there are at least a hundred COVID-19 vaccines based on the platform technology in various stages of clinical development and deployment [3]. To explore the rationale behind the transition toward novel platform-based vaccines, this paper compares the traditional and the novel biotechnology platform-based vaccine manufacturing techniques and reviews the existing COVID-19 vaccine manufacturing scenarios (Secs. 2 and 3).

According to a recent study [4], the vaccines developed under the novel platform concept such as the Moderna, Pfizer/BioNTech (messenger ribonucleic acid vaccines), and Sputnik (viral vector vaccine) were found to be very effective in protecting against COVID-19 with the effectiveness of 88.7%, 83.3%, and 85.7%, respectively. It is worthwhile to note that these vaccines were developed just by using the genetic sequence information of the virus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). It is projected that these remarkable platform techniques can be easily extended, restructured, and redesigned to develop future vaccines to treat a wide range of contagious diseases [5,6]. Once these vaccines are tested to be safe and effective, large-scale production of future vaccines in short periods of time can be realized.

Ulrich and Eppinger [7], in their well-respected work, developed a standard for the classification of products based on their underlying characteristics. According to the Ulrich and Eppinger classification, traditional vaccines were classified into one group: high-risk products. The COVID-19 vaccines based on the novel biotechnology platforms, on the other hand, have more features than a traditional vaccine and span multiple categories of Ulrich and Eppinger's product classification, such as modular product, quick build product, and high-risk product. To emphasize this versatility of the novel COVID-19 vaccine as a "product" and to make an effective comparison of its characteristics with traditional vaccine products, the well-established Ulrich and Eppinger product classification was used as a reference framework (Sec. 4). By this multi-group classification, it is possible for the biopharmaceutical industries to appropriately identify and apply strategies such as modular manufacturing, mass customization, automation, and knowledge management to boost the vaccine development and manufacturing process.

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Finally, the paper presents the future possibility of incorporating the smart manufacturing paradigms with the novel platform-based manufacturing process (Sec. 5). It is hoped that this study would serve as a valuable asset for the biopharmaceutical firms to appropriately streamline their policies, resources, and goals to meet the global vaccine requirements.

This paper is a modified and updated version of the conference paper titled "Towards Smart Vaccine Manufacturing: A Preliminary Study during Covid-19" [8] that has been presented at the ASME International Mechanical Engineering Congress and Exposition 2021.

2 Traditional Methods for Vaccine Manufacturing

A vaccine is usually made from a very small amount of dead or weak germs like bacteria, viruses, etc. that can cause diseases. The vaccine helps the body fight against diseases effectively and quickly so that the person will not get sick [9]. Different diseases require different vaccines, and hence, scientists have created a variety of vaccines. Traditionally, vaccines have been classified into the following groups:

(1) *Whole Virus-Based Vaccines*: Vaccines of this kind consists of either (1) virus that has been inactivated by chemicals or radiation, or (2) a live virus that is modified and weakened so that it induces an immune response but does not cause disease [10].
(2) *Protein-Based Vaccines*: This consists of a protein purified from either (1) virus or virus-infected cells, or (2) virus-like particles (VLPs), which are complex proteins that adopt a virus-like confirmation but do not contain a virus genome [10].

The vaccines made from these groups have been successful in controlling and eradicating many diseases worldwide [11]. COVID-19 vaccines such as Covaxin from Bharat Biotech, Coronavirus-Like Particle COVID-19 (CoVLP) from Medicago Inc., NVX-CoV2373 from Novavax, and COVI-VAC from Codagenix/Serum Institute of India are examples of vaccines made using the traditional method with the inactivated virus [3]. Table 1 shows some of the traditional vaccine types, corresponding licensed vaccines, and corresponding COVID-19 vaccines in various phases of clinical development.

2.1 Vaccine Manufacturing: Traditional Method. This section describes the traditional way of vaccine development and manufacturing that has been in practice since the introduction of the concept of vaccines. The vaccines manufactured using these techniques are the traditional vaccines involving the injection of some form of the disease-causing pathogen either attenuated or inactivated [13].

Vaccine development follows a phased procedure and can take a long time to assess safety and efficacy, clear all the regulatory approval procedures, and finally manufacture in a large scale for widespread vaccine supply and distribution. The complete process typically takes about 5–10 years and is composed of two phases: product development phase and production phase [13]:

(1) *Product Development Phase*: The vaccine development process involves taking an antigen that is identified to be the best candidate from research and then transforming this into the final product. In this process, the vaccine ingredients, processing materials, specifications of the product, and manufacturing process are determined and defined. The scale of manufacturing during this phase is significantly less than what is used in the mass production phase. Vaccines for clinical trials are usually developed in this phase.
(2) *Production Phase*: The production is composed of two stages. In the first stage, the "Drug Substance" is created, and in the second stage, the "Drug Product" is created [14]. The drug product is the formulated active ingredient that is administered to the patients.

Table 1 Selected traditional vaccine types and licensed vaccines (as of Dec. 1, 2021) [3,11,12]

Traditional vaccine type	Licensed vaccines	COVID-19 vaccines
Live attenuated virus	Small Pox, Polio	COVI-VAC
Inactivated virus	Influenza, Hepatitis A	Covaxin
Protein subunit	Acellular Pertusis	NVX-CoV2373
Virus-like particles (VLPs)	Hepatitis B	CoVLP

The Product Development and Production Phases are illustrated in Fig. 1 and discussed in some detail below.

2.1.1 Stage 1: Production of Drug Substance. The first step in Stage 1 production is called the cell culture. The aim of this step is to generate the antigen which is required to induce an immune response. In this step, a living host that can produce the antigen is cultivated. Different hosts may be used depending on the type of antigen that will be expressed. In the case of traditional vaccines made from live or attenuated viruses, often the host is a chicken fibroblast and for recombinant protein antigens, the host may be bacterial, yeast, or mammalian cells [13]. These cell cultures are often referred to as "master cell banks" and are rigorously characterized, stored, and protected [13]. Using this cell bank, working cell banks can be prepared for future production. It is important to note that any changes in the cell bank used for production can result in changes in the final product, so cell growth is rigorously controlled.

The next step is to release or separate the antigen from the substrate, and this is often called the harvesting process. Once again, this is done in different ways depending on the type of the host. It could be separation of the free virus or isolation of proteins secreted in a cell or removal of the cell from the spent medium. Once the antigen is harvested, it is sent for the purification of the antigen. In this step, all the impurities are removed. For vaccines

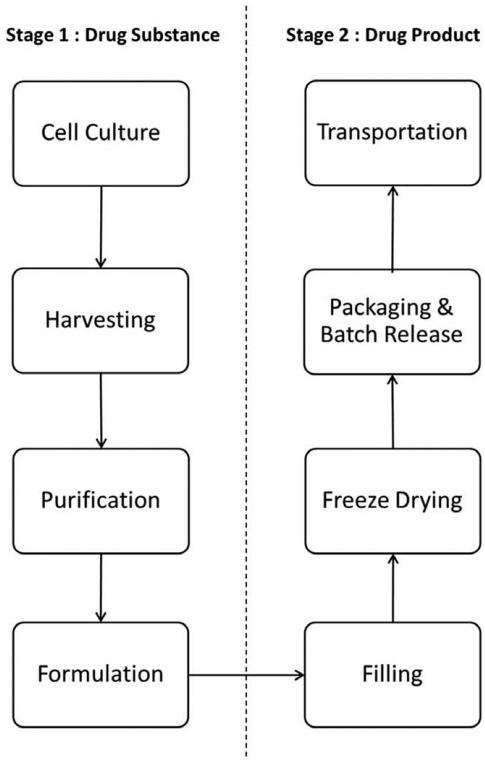

Fig. 1 Workflow of the traditional vaccine manufacturing process

produced from recombinant proteins, this process might also consist of column chromatography and ultrafiltration [13]. In the case of inactivated viral vaccines, this step might just involve inactivating any live virus used to produce the vaccine or inactivating any contaminating viruses that came along with the host cells.

Once the antigens or inactivated viruses are purified, they are combined with all the individual components and ingredients that constitute the final vaccine. This step is called the formulation. The ingredients added in this step might be the stabilizers to improve shelf-life, adjuvant to boost immune response, or preservatives to protect vaccines from external interactions. These operations are always carried out in a controlled environment [13].

2.1.2 Stage 2: Production of Drug Product. This stage mostly comprises the postproduction activities after the vaccine has undergone the formulation process. The vaccines after Stage 1 are filled into a vial or a syringe. Then, it is subjected to freeze-drying, where water is removed from the product by converting it to a powder form. This ensures better stability. The vials are then labeled according to the regulatory requirements and packed; this is the packaging process. Next, the quality assurance checks and confirms that the vaccine has been manufactured and tested according to the standards. After the final approval, the product is authorized for batch release and distribution. Finally, the vaccines are transported in a temperature-controlled environment around the world. This completes the entire vaccine manufacturing process.

2.2 Challenges With Traditional Methods. Traditional vaccines have some serious drawbacks. First, the vaccines involve a lengthy culturing process in addition to the considerable time lag between the antigen production and the last mile delivery of vaccines. Furthermore, owing to the contagious nature of the ingredients, traditional vaccine manufacturing requires sophisticated containment facilities and intense safety precautions to minimize the risk to the operators and environment. Another concerning factor is that despite the efforts to modify or weaken the virus to create vaccines, live attenuated viruses can revert to their virulent strains [15].

The traditional vaccine manufacturing process also has several limitations due to the large number of steps involved in this process. None of the vaccine manufacturing processes are optimal, and hence, there is always a loss of material that reduces the overall productivity. An additional challenge with vaccine manufacturing is the necessity to comply with the WHO guidelines on safety and manufacture according to the current Good Manufacturing Practices (cGMP) [13].

Moreover, traditional vaccine manufacturing typically involves the collaboration of multiple organizations (contract manufacturers) which are individually responsible for a particular segment or process in vaccine manufacturing. Hence, there are often inefficiencies with proper coordination among the parties especially with respect to compliance with the safety and quality guidelines and obtaining the required regulatory licenses. Finally, traditional manufacturing always has issues with adapting to the changing demand of vaccines and responding to the changes quickly and effectively. The production rate needs to be scaled up especially during pandemics and needs to be brought back when things subside. This often calls for production flexibility which is not easily attainable in the traditional manufacturing setting.

Outbreaks of pandemics such as the COVID-19 are timely signals that an improved vaccine manufacturing process is required to reduce vaccine development and production time. COVID-19 vaccines based on novel biotechnology platforms such as the mRNA and viral vector vaccines [16] are the first step toward this goal. It is worthwhile to note that during the COVID-19 pandemic, many biopharmaceutical industries have successfully transitioned to the novel platforms to develop vaccines on a much faster timeline without compromising on vaccine efficacy or safety.

3 Novel Biotechnology Platforms for Vaccine Manufacturing

In an adverse outbreak of a pandemic like the COVID-19, the typical timeline of vaccine development, manufacturing, and distribution needs to be accelerated to control the spread of the disease. Biopharmaceutical firms responding to this need require significant financial resources and an expedited pathway for approval of the vaccine products by the Food and Drug Administration (FDA). To support such firms, the US government initiated a public–private partnership under the Operation Warp Speed (OWS). OWS supports the mass production of vaccines and underwrites the financial commitment that allows companies to scale vaccine production without waiting for full Phase 3 clinical trial results. Vaccine manufacturers have received billions of dollars in funding to support vaccine scale-up through this effort [17].

The traditional vaccine manufacturing techniques, however, can no longer meet the sudden spike in demand. This has motivated the biopharmaceutical industries to shift to modern vaccine manufacturing methods using viral vector or nucleic acid-based (i.e., mRNA) vaccines. During the ongoing COVID-19 pandemic, biopharmaceutical industries have successfully employed the novel vaccine platform technology to develop and manufacture vaccines on an accelerated timeline without compromising on vaccine safety, efficacy, and scientific or ethical integrity. This has been demonstrated by firms using mRNA vaccines based on the platform technology as observed from the following case studies.

3.1 mRNA Vaccines Case Study 1: Pfizer/BioNTech COVID-19 Vaccine Manufacturing. Pfizer/BioNTech vaccine, developed by BioNTech in partnership with Pfizer, was the first vaccine to be granted both Emergency Use Authorization (EUA) and Full Approval (licensed) by the US Food and Drug Administration (FDA). It is an mRNA vaccine composed of nucleoside-modified mRNA that encodes the spike protein found in the SARS-CoV-2 and is encapsulated in lipid nanoparticles [18]. Figure 2 shows the workflow of the mRNA vaccine from Pfizer/BioNTech.

Vaccines are being manufactured by Pfizer in their own facilities by employing a three-stage process. In the first stage, the deoxyribonucleic acid (DNA) that codes the spike protein of the

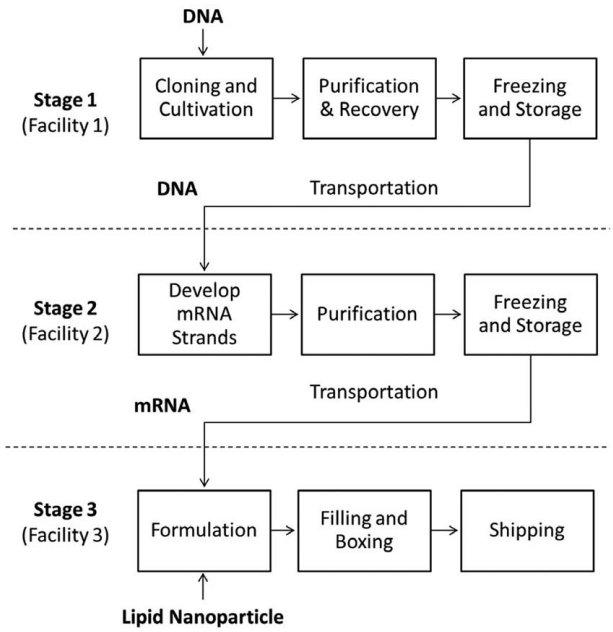

Fig. 2 Workflow of the mRNA vaccine manufacturing process (Pfizer/BioNTech)

SARS-CoV-2 is introduced into E. coli bacteria. This is conducted at a plant in Chesterfield, Missouri [19]. The bacteria are harvested after 4 days of growth, and the desired DNA is recovered through rigorous purification. The genetic material is then stored under freezing conditions and transported to a Pfizer plant in Andover, Massachusetts for the second stage [20].

In the second stage, the genetic information encoded in the DNA is transcribed by enzymes to make messenger RNA (mRNA) working copies. These mRNA copies ultimately are the instructions to create the spike protein antigens in vaccinated people. The mRNA pieces are then purified, frozen, and stored in bags [21]. The bags are then shipped to the next Pfizer plant in Portage, Michigan for the final stage of the manufacturing [22]. In this third and final stage, the mRNA pieces are combined with lipid nanoparticles [21]. Pfizer has signed contracts with partner chemical firms for lipid nanoparticle supply [23]. Once the mixture is made, it is then filled in vials, boxed, and frozen [21]. Pfizer has developed temperature-controlled shippers for the safe transport of vaccines. The thermal shippers are designed to use dry ice to maintain the cold temperature. The boxes are planned to be delivered by both air and ground transport to the site where they will be administered [22]. According to reports [21], the major bottleneck in the entire manufacturing process is the step involving the mixing of mRNA and lipid nanoparticles. This is attributed to the fact that the company was unable to wait until the procurement of large-scale machinery and was forced to use existing processes. Also, the main issue with the transportation of this vaccine is that it needs to be maintained at extremely cold and freezing temperatures (between −80 and −60 °C). This proves to be a great challenge in countries that lack extreme refrigeration facilities.

3.2 mRNA Vaccines Case Study 2: Moderna Vaccine Manufacturing. Moderna vaccine is also an mRNA vaccine that was given an EUA by the FDA soon after the Pfizer/BioNTech vaccine. Moderna vaccines have similar efficacy as its counterpart and, more importantly, requires a storage temperature of just 2–8 °C for up to one month or −20 °C for longer periods, as opposed to the more extreme freezing temperature requirement of Pfizer/BioNTech vaccine.

Moderna follows similar manufacturing steps like its counterpart but has entered more extensive collaborations with contract manufacturing organizations (CMO), when compared with Pfizer/BioNTech, to scale up its vaccine production. Moderna has involved the Lonza group to manufacture additional vaccines in their facilities and is purchasing the lipid nanoparticle from Corden Pharma. It has contracted with Catalent in the United States for the task of filling and packaging [24].

The remarkable platform-based vaccine design and manufacturing technique used by these firms have some similarities with the traditional product design and manufacturing concepts and interesting features applicable to a large class of products beyond traditional biopharmaceutical products. To highlight the "smart" characteristics of these novel platform-based COVID-19 vaccine products and to make an effective comparison with the traditional products, a well-established product classification framework is used as a reference. This is discussed below, in Sec. 4.

4 Analysis of COVID-19 Vaccine Products and Manufacturing

According to Ulrich and Eppinger [7], products generally can be classified into eight types based on the underlying generic product development process as shown in Table 2. On close examination, it can see observed that the novel vaccine products do not just fall under one of the classifications shown in Table 2, but instead can combine many types of classifications. Therefore, the novel platform-based vaccines can be effectively classified as:

(1) *Platform Products*: This is the terminology used by WHO and in medical literature. For example, the Pfizer/BioNTech and Moderna vaccines belong to the same platform because they share the same biotechnology for (1) making mRNA strands and (2) encapsulating them in lipid nanoparticles.
(2) Process-Intensive Products: The production processes for these vaccines are extremely intricate and are highly controlled and regulated by the FDA.
(3) *Technology Push Products*: The biotechnology used for many of the vaccines is relatively new—they are based on recent advances in molecular biology and genomics.
(4) *High-risk Products*: Drug trials have a high risk of failure.
(5) *Customized Products*: Slight variations of the vaccines (e.g., mRNA) are being tried now to combat the emerging virus variants.
(6) *Quick-Build Products:* Rapid "design-build-test" of vaccines is being tried now to combat the emerging virus variants.
(7) *Complex System Products*: The development and manufacturing of these vaccines involve close intervention between both hardware and software components. Any modification in the gene-sequencing software can induce changes in the vaccine development and manufacturing process.

The detailed information on each of the above classifications is discussed below under separate sub-sections. Sections 4.1 and 4.2 contain a detailed analysis of the concepts of "platform products" and "process-intensive product" applied to the novel platform-based vaccine products, respectively. The notion of technology push products is discussed along with platform products since Ulrich and Eppinger [7] consider these concepts to be very similar. Vaccines as high-risk products are quite self-explanatory considering the liabilities associated with the use of such products. Moreover, vaccines are becoming highly "customized products" and "quick-built products", and these ideas are assessed in Secs. 4.3 and 4.4, respectively. Finally, Sec. 4.5 describes how vaccines fall into the category of complex system products.

Table 2 Classification of products by Ulrich and Eppinger [7]

Type	Description	Example
Generic (market-pull) products	The team begins with a market opportunity and selects appropriate technologies to meet customer needs	Sporting goods, furniture, tools
Technology-push products	The team begins with new technology, and then finds an appropriate market	Gore-Tex rainwear, Tyvek envelopes
Platform products	The team assumes that the new product will be built around an established technological subsystem (a technology platform)	Consumer electronics, computers, and printers
Process-intensive products	Characteristics of the product are highly constrained by the production process	Snack foods, breakfast cereals, chemicals, and semiconductors
Customized products	New products are slight variations of existing configuration	Motors, switches, batteries, and containers
High-risk products	Technical or market uncertainties create high risks of failure	Pharmaceuticals, space systems
Quick-build products	Rapid modeling and prototyping enable many design-build-test cycles	Software, cell phones
Complex systems	System must be decomposed into several subsystems and many components	Airplanes, jet engines, and automobiles

4.1 Vaccines as Platform Products. Platform-based vaccine has emerged as the best option to tackle the COVID-19 vaccine manufacturing challenges, which include speed, efficacy, and safety. In simple terms, a product platform is a "group" of distinct parts, components, or modules that is common to all the products derived out of the platform. For example, an automotive industry might develop a car platform, where all the vehicles manufactured in this platform will have the same chassis, powertrain, drive train, battery, etc. These components, which are shared among the different car models, define the platform components and the platform components that constitute the platform.

Platform-based vaccines support modularity. For example, the vaccines can have a "base carrier" such as lipid nanoparticles or viral vectors. The components that are plugged into the base carrier are called "modules." The modules can be the mRNA or DNA strands, which are tailor-made based on the target disease and can be enveloped by the base carrier to generate the required vaccine [15]. Once a platform has been licensed for a vaccine, the development of new vaccines in the future, using the same platform, will enable rapid development, regulatory approval, and large-scale manufacturing.

There are mainly two kinds of platform-based vaccines that are being widely used to combat COVID-19: Viral Vector vaccines and mRNA vaccines, which are explained in detail below. It is worthwhile to note that the notion of the vaccine platform is very similar to the traditional product platform concept. The benefit of these vaccines is that they do not contain the actual disease-causing pathogen in any form. This enables protection from the disease without being at risk of infection.

Viral vector vaccines use an altered version of a harmless virus, called the vector, to deliver DNA (instructions) to our body. After entering our cells, this vector carrying the DNA gets into the cell nucleus. Inside the nucleus, the DNA is transcribed to mRNA. The mRNA exits the nucleus, where the cell machinery translates the mRNA to a harmless piece (usually a protein) of the virus that causes the disease. The immune system gets triggered by this foreign piece and tries to get rid of it. This helps our body develop the ability to prevent future infection from the same kind of virus [25]. Vaccines based on the viral vectors have a base platform carrier that is usually a harmless virus (vector) onto which the DNA is embedded to create the vaccine. By tweaking the DNA information, a new vaccine can be quickly developed by combining the modified DNA onto the base platform carrier as shown in Fig. 3. Table 3 shows selected COVID-19 viral vector vaccines in clinical development according to the WHO database, including the ones Fully Approved (Licensed) and those under the Emergency Use Authorization (EUA) by various governments.

Table 3 Selected COVID-19 viral vector vaccines in various development phases (as of December 1, 2021) [3]

Developers	Phase
AstraZeneca + University of Oxford	EUA (UK)
Janssen Pharmaceutical	EUA (USA)
Vaxart	Phase 1
University of Munich	Phase 1

Table 4 Selected COVID-19 mRNA-based vaccines in clinical development phase (as of December 1, 2021) [3]

Developers	Phase
Pfizer/BioNTech + Fosun Pharma	Full approval (licensed) (USA)
Moderna + NIAID	EUA (USA)
CureVac AG	Phase 3
Imperial College London	Phase 1

mRNA vaccines, on the other hand, consist of mRNA (messenger RNA) strands that help our immune system learn to fight a disease without injecting in any kind of germ. The mRNA contains instructions on how to make a harmless piece (usually a protein) of the pathogen. Once the mRNA vaccine is inside our cells (but outside the nucleus), the cells decode the instruction and create the protein. This protein is then identified by the immune system which then fights to neutralize the foreign piece, thereby developing the ability to tackle future infections [25].

Table 4 shows selected COVID-19 mRNA vaccines in clinical development according to the WHO database, including the ones authorized for emergency (EUA) use by various governments. As shown in Fig. 4, vaccines based on this category have a base platform carrier, usually lipid nanoparticles, onto which the mRNA is embedded. By tweaking the mRNA information, a new vaccine can be quickly developed by combining the modified mRNA onto the base platform carrier.

The immense necessity to manufacture COVID-19 vaccine has led to tremendous investments to configure vaccines based on

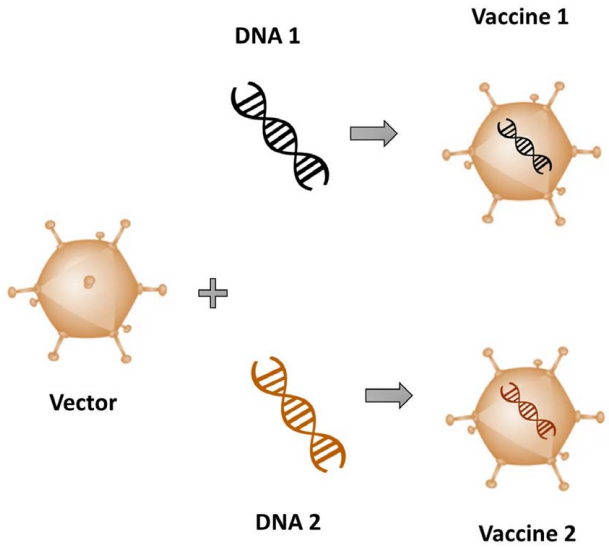

Fig. 3 Two different DNA sequences can be used with the same base platform carrier (vector) to form two different viral vector vaccine products

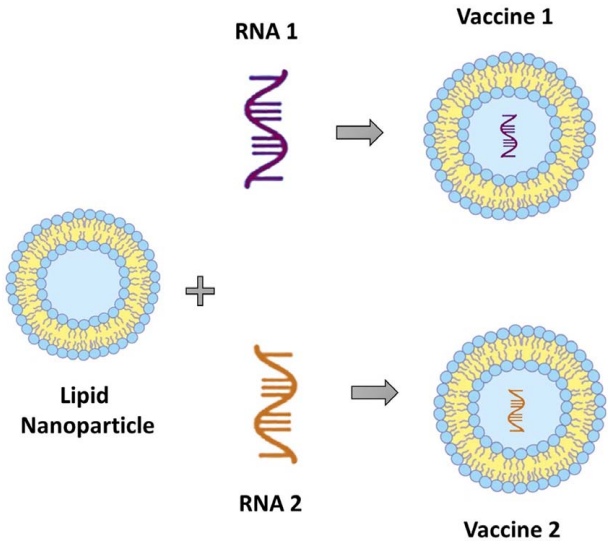

Fig. 4 Two different RNA sequences can be used with the same base platform carrier (lipid nanoparticle) to form two different mRNA vaccine products

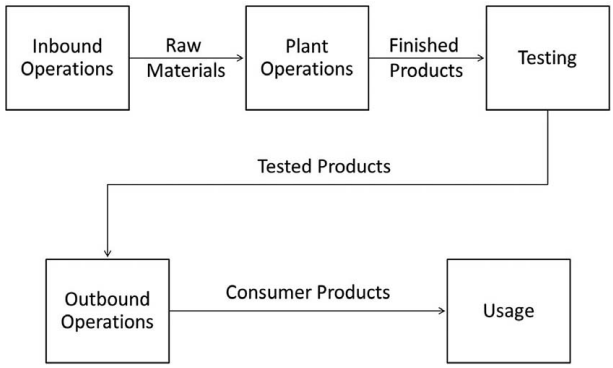

Fig. 5 Generalized work flowchart for vaccine development and manufacturing

modular architecture like these in recent times. In this regard, the term biotechnology platforms has gained a lot of attention among pharmaceutical companies. The main reason is that the product platforms could be quickly redesigned to meet a different specific need.

4.2 Vaccines as Process-Intensive Products. Ulrich and Eppinger [7] define Process-Intensive Products as those which have well-defined constraints on the product properties such that the product and production process design cannot be separated. In many cases, the processes involved in product manufacturing have a lot of limitations and this controls the design of the product to some extent. In addition to this, manufacturing processes involved with the production of vaccines are extremely complex and are strictly regulated by agencies such as the FDA. This can be observed from the COVID-19 vaccine manufacturing case studies described in Secs. 3.1 and 3.2. Hence, vaccines can be categorized as extremely process-intensive products. In this regulation-driven manufacturing, we need to have systematic checks for traceability and approval process. Information thus generated is collected, transmitted, and stored as we move along the manufacturing process. This adds to the complexity of designing and controlling the vaccine manufacturing process. If we want to model and control the process, we need to identify the different variables that can be controlled and observed in each step of the vaccine manufacturing process. Figure 5 shows a general process flow in vaccine development and manufacturing.

The variables that can be observed and/or controlled in each of the process steps are listed in Table 5. It might be worthwhile to note that the vaccine manufacturing process involves ingredients such as large biomolecules. Living cells serve as the factories for producing such large molecules. Since the largest of such molecules are very small on the submicron scale, there are significant observational and measurement challenges.

If it is not possible to observe a state of a system and hence unable to measure it directly, the question rises as to how one can properly control these processes to perform quality checks. This leads to the concept of developing mathematical models and estimates based on theories, experiments, experience, or other reliable sources. In other words, when the state of a system is not observable, we need to estimate with mathematical models using the inputs and correlated variables that we can measure. These models help derive indirect measurements.

Aström and Murray [26] have developed methodologies to build such a model to estimate $\hat{x}$ of the unknown state of the system when the observer is able to measure a process output y (along with a noise n) and the input u. The block diagram illustrated in Fig. 6 depicts this concept. Here, the state of the system not observable is x. The block "observer" establishes a correlation between the unknown state and measurable variables. It might be worthwhile to note that models, even though might solve the immediate issues, still pose additional challenges in vaccine manufacturing, which are yet to be addressed.

4.3 Vaccines as Customized Products. As the COVID-19 vaccines are being manufactured and distributed in a large scale aiming to control the pandemic, new variants of the SARS-CoV-2 have been identified in the United Kingdom (B.1.1.7—Alpha variant), South Africa (B.1.351—Beta variant and B.1.1.529—Omicron variant), Brazil (P.1—Gamma variant), and India (B.1.617.2—Delta variant). These variants, designated as "variants of concern" by the WHO [27], are known to have spread into various parts of the United States. Researchers are of the opinion that the mutated virus might be able to evade or undercut the effectiveness of the existing vaccines. This might imply that the first generation of the COVID-19 vaccines would need an update.

Developing and manufacturing an updated vaccine to target the mutated virus in the traditional way would require cultivating the mutated virus and then highly attenuating or inactivating them. This process could consume a tremendous amount of time and might not be a feasible solution to control the outbreak of another pandemic. However, this is not the case with novel vaccine platforms. The COVID-19 vaccines made by Moderna and Pfizer/BioNTech, for instance, use mRNA in the base platform and instruct the body to produce the spike proteins found on the virus. These manufacturers point out that novel platform-based vaccines give them the ability to swap the module—the coding region of the mRNA candidate (the instructions to create the protein)—to match the mutated virus and plug it into the base carrier of the first-generation vaccine to quickly develop the updated vaccine.

Scientists are also trying to gauge the possibility of including both the old and new forms of the protein in one shot to develop a multivalent vaccine [28]. All these options are made possible by the vaccine platforming approach, thereby making the vaccine manufacturing process more agile and adaptable. This could be considered as the "smartness" of the novel vaccine manufacturing process, and hence, these novel platform-based vaccines can be considered as highly customizable products.

4.4 Vaccines as Quick-Build Products. The main resource required for the development of novel platform vaccines is the genetic sequence of the new virus. The genetic sequence of the virus, once generated, can be rapidly shared across the globe in the digital format. This information can be then used globally to develop and manufacture vaccines at incredible speeds. According to reports [29–31], Moderna and Pfizer/BioNTech had conducted Phase 1 trials within approximately 2 and 3 months, respectively,

Table 5 Variables in each stage of vaccine development and manufacturing phase that can be observed or controlled

Stage	Variables
Inbound	Raw materials/Ingredients—Quality, Types, Quantity, Storage—Type, Duration, and Location
Plant operations	Type of Machine/Equipment, Cycle Time, Environment Factors, Machine Properties, Temperature, Process Steps, Energy Consumption, Production Layout, Machine Parameters, and Efficiency
Testing	Product properties (composition), Temperature, and Contaminations
Outbound	Temperature/Environment, Packaging, Transport Type, Duration, Storage, Batching, and Handling
Usage	Efficacy, Duration/Life

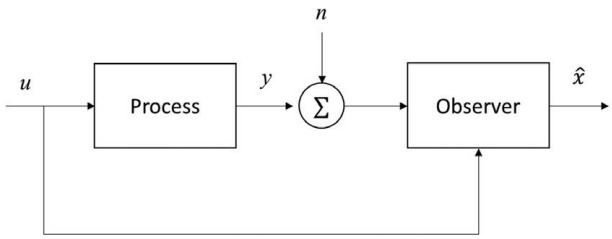

Fig. 6 Developing estimate $\hat{x}$ of an unobservable state of the system x with input u, noise n, and measurable process y [26]

after sequence selection and the entire vaccine development process from preclinical study to the emergency authorization by the FDA was completed in about 12 months. It is worthwhile to recall that a traditional vaccine development following the same steps would typically take around 10–15 years. Figure 7 shows a comparison of the timeline for COVID-19 vaccine based on platform technology versus the projected timeline for a vaccine if developed using the traditional approach. As we can observe from Fig. 7, the time gained with the novel platform-based COVID-19 vaccine development approach when compared to the traditional approach, separately for each step would be roughly 2 years each and in total about 10 years.

As the highly contagious SARS-CoV-2 variants such as the B.1.617.2 (Delta variant) began to spread widely across the globe, vaccine manufacturers such as BioNTech have started developing new versions of COVID-19 vaccines targeting the variants. Since the COVID-19 vaccines are based on novel platforms, updated vaccines targeting the variants can be easily developed by changing the genetic sequence appropriately, within a timeframe as short as four weeks [32]. These remarkable achievements underline the fact that novel platform-based vaccines can be classified as quick-build products.

Additionally, huge cost and time savings can be achieved by bypassing steps including cell culture, harvesting, inactivation, and formulation during vaccine development and manufacturing. Bypassing these steps also help in the reduction of overall cycle time, thus enabling rapid manufacturing of platform vaccines. It has been reported that United Kingdom has introduced "human challenge trials" where healthy people are exposed to COVID-19 virus to identify the effect of the virus on humans and the effectiveness of vaccines [33]. These trials, which have been launched after substantial ethical review, are expected to give doctors vital information regarding COVID-19 disease and the virus, an important input to the vaccine development process. Hence, rapid development and manufacturing of vaccines along with quick trials can make the vaccine essentially a quick-build product.

4.5 Vaccines as Complex System Products. In recent times, the concept of Cyber Physical Systems (CPS) has been widely used in the field of robotics, aviation, automotive systems, industrial control systems, etc. In a typical CPS, the hardware and software components are deeply integrated and closely interact with each other [34]. Some examples of CPS include autonomous cars, smart grids, and autopilot avionics. The adoption of CPS is on the rise, and now, we observe their application in biopharmaceutical products such as the novel platform-based vaccine. In the early stages of COVID-19 pandemic, researchers had used "genomic sequencers" to sequence the virus causing SARS-CoV-2. Using this sequence, researchers were then able to select the appropriate gene that goes into the novel platform-based vaccine. This process involves a lot of cutting-edge software and bioinformatics approaches [35]. When new virus variants are detected, researchers can make appropriate modifications in the software code to change the gene sequence that goes inside the vaccine so as to update the vaccine. Additionally, the gene sequences can be shared globally with other researchers so that better analysis of viruses and diseases is possible [35]. Therefore, the novel platform-based vaccine

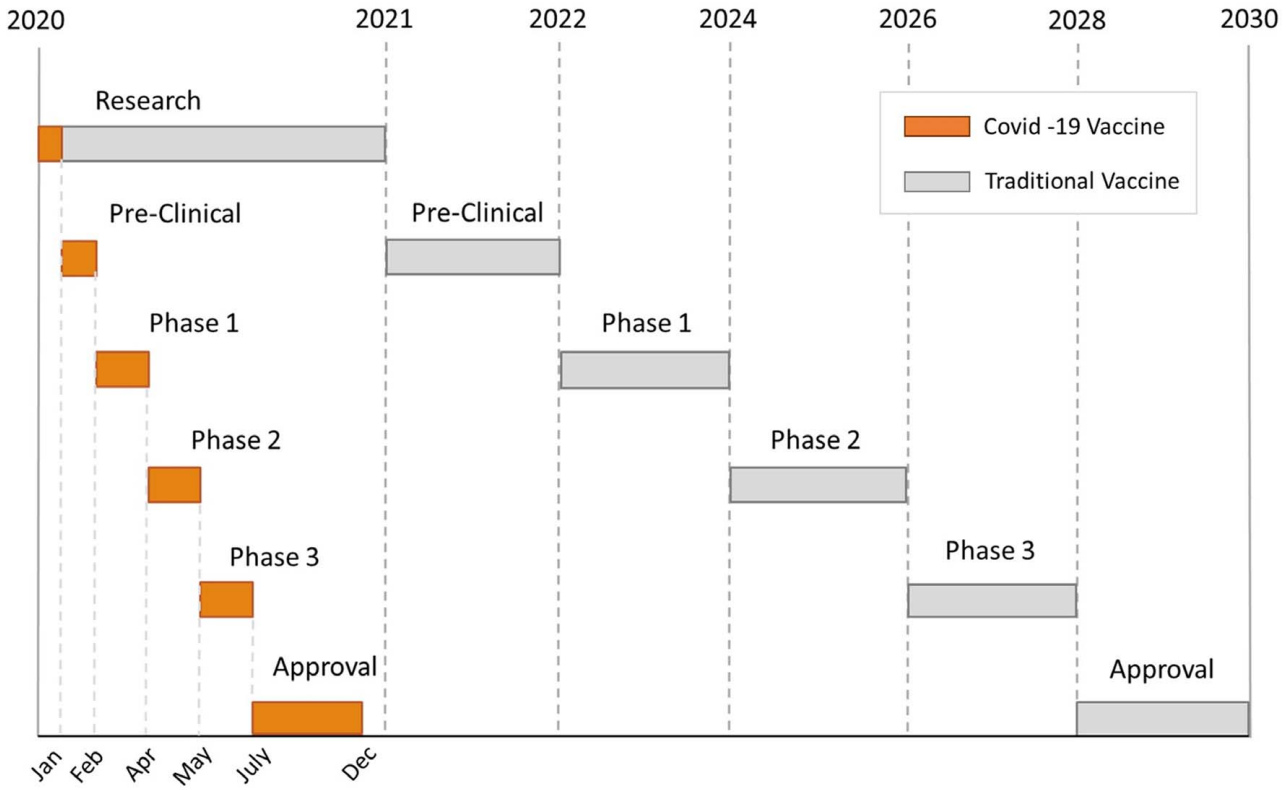

Fig. 7 Comparison of the development timeline for a novel platform-based COVID-19 vaccine and a projected timeline for a vaccine following traditional methods

development and manufacturing involves close intervention between both hardware and software components. Any modification in the gene-sequencing software can influence and induce changes in the vaccine development process. This makes the novel vaccines complex when compared to the traditional vaccines.

The observation that the novel vaccine products fall into seven out of eight product classification types proposed by Ulrich and Eppinger [7] is beneficial for the analysis and future development of the vaccine as a product. Most of the generic products, including the traditional vaccines, fall only under one of the eight categories, making them less robust and flexible for future improvements. However, novel vaccine products that span across multiple categories are more robust and flexible and offer more degrees-of-freedom. Hence, they support rapid customizations and modifications. This is very important for vaccine products since the use cases for vaccines are dependent on the pathogens, which constantly evolve and mutate.

5 Future of Smart Vaccine Manufacturing

Vaccine manufacturing often employs a series of process steps. The manufacturing process and the workflow for each type of vaccine might involve different process steps implemented in different sequences. This might pose some unique challenges with respect to setting up the manufacturing facility. For example, there is a challenge with the scaling up of the viral vector vaccines since new facilities are still under construction [36]. However, some of the challenges in vaccine manufacturing are similar to those that are addressed by the broader manufacturing community under the concept of smart manufacturing, which is essentially a transformation to digital and advance manufacturing techniques. Some of these concepts are discussed below with specific applications to the biopharmaceutical industry.

5.1 Digitalization of Biopharmaceutical Industry. The most important features of smart manufacturing include digitalization of the complete manufacturing enterprise with enhanced productivity and seamless information exchange through densely connected devices and intelligent control [37]. Digitalization can transform the industry by enhancing customer experience, modernizing operations, and revolutionizing business models [38]. Recent and emerging technologies such Internet of Things (IoT), Augmented Reality (AR), etc., are key players in this era of digitization and provide ubiquitous information exchange between people, machines, and even industries.

In the context of biopharmaceutical industry, adoption of IoT would mean the adoption of *smart devices* (such as sensors, actuators, microcontrollers, and Radio-frequency Identification devices) to capture, store, and transmit data and *services* (such as mobile and web applications) to facilitate connections between devices during each stage of the vaccine development and manufacturing process. The smart devices would be able to track the temperature of the vaccine products, ingredients and compositions and assign unique identifiers to vials for future reference. Cloud-based applications such as Amazon Web Services IoT can be used to develop applications to monitor and analyze the data being generated at each stage.

The AR technology also opens new opportunities for digitalization in the biopharmaceutical industry. AR devices such as Microsoft HoloLens, Google Glass and so on can access data from its inbuilt sensors, internal storage, and connected devices and combine them with the operator's field of view and environment. Features such as gesture control help the wearer interact with other devices and products to obtain its properties. For instance, AR devices can be used to identify the serial number of a specific vaccine product by interacting with it using gestures [38].

5.2 Other Enabling Technologies. The biomanufacturing roadmap by BioPhorum Operations Group (BPOG) has identified a few enabling technologies and capabilities [39] for embracing smart manufacturing. Some of these can be applied to the biopharmaceutical industry and are discussed below:

(1) *Automated Facilities*: This aims for reducing human interaction and improving the quality of production through automation. In recent times, contaminants were found in the COVID-19 vaccine manufactured by a few biopharmaceutical companies [40,41]. Large quantities of vaccines are thrown away during the manufacturing process and/or after manufacturing due to the presence of contaminants, and this often raises safety concerns. In many cases, contaminations in the vaccine are reported due to mishandling by humans during the manufacturing process. Hence, by automating the process, reducing human interaction, or increasing direct robot–human interaction in a shared space, the quality of the vaccines could be improved. Moreover, there would be higher production rates, efficient use of materials, and improved safety. In this regard, automating the facility using robots, collaborative robots (cobots), self-driving vehicles along with digital enablers such as IoT, Artificial Intelligence etc., would be a plausible solution.
(2) *Modularity and Mobility*: By creating multiple modules out of the manufacturing process framework, steps including the standardization, validation, configuration, testing, and assembly become easier. For instance, Pfizer manufacturers vaccines through a three-stage process conducted at different facilities, thus creating independent modules out of the complete manufacturing framework [19–22]. Moreover, it enables mobility of the facility, when needed.
(3) *Knowledge Management*: With the integration of product and process knowledge, the quality of the product increases and development cost decreases. For example, the adoption of tools to document product and process knowledge, sharing knowledge resources between facilities, and documenting lessons learned from previous experiences will result in efficient manufacturing, fewer error, and lower costs. Additionally, well-structured and documented information and its management using digital technology will boost easy access of information when needed. This increases the speed and quality of the process.
(4) *Supply Chain Management*: A good outline for the supply chain is only possible through seamless information exchange and trust between collaborators, including the end-users. According to a survey [42], about 77% of the US citizens are extremely concerned regarding the efficacy and, more importantly, the safety of vaccines. Hence, a holistic approach is essential to infuse transparency, speed, and accountability across the vaccine supply chain and distribution system. In this context, the concept of "Blockchain," which is a digital record-keeping technology, has gained considerable attention. Vaccine supply chain networks powered by blockhain technology enable manufacturers to monitor for adverse and unforeseen events, and distributors to gain more visibility and better ability to manage supply chain disruptions [42]. Moreover, this technology also enhances vaccine safety monitoring including counterfeit detecting, thereby building trust among the public.

It is expected that the smart manufacturing paradigm will complement the efforts to create vaccines at "lightning speed." Additionally, the concept of product platforming discussed in the previous section could be incorporated into the smart manufacturing techniques to transform the entire biopharmaceutical sector. However, there are a few barriers such as lack of urgency, economic constraints, limitations with technology infrastructure, unclear company vision, lack of efficient leadership, ambiguity with the ownership, privacy, and security of data [38–43] that need to be overcome. Working toward this goal, the International Society for Pharmaceutical Engineering (ISPE) is in the process of creating help resources and roadmap to implement Industry 4.0 techniques in the

biopharmaceutical sector through a new concept termed as Pharma 4.0 [44]. As the vaccine manufacturing companies strive to improve their productivity and better respond to healthcare requirements, the adoption of many smart manufacturing techniques could thus help address several challenges that one might encounter.

6 Concluding Remarks

The vaccine development and vaccine manufacturing methods have a strong connection and have advanced together. The main driver for the vaccine production technology is to make vaccines quickly and safely in a cost-effective manner that would facilitate worldwide distribution. To materialize this, especially in the wake of the COVID-19 pandemic, numerous biopharmaceutical industries have now switched over from traditional techniques to innovative platform-based technologies.

To bring out various aspects and characteristics of the novel COVID-19 vaccine development and manufacturing, Ulrich and Eppinger [7] classification of products was used as a framework. By leveraging the idea of product platforms, new vaccines could easily be customized by switching the genetic information. This can be very beneficial when trying to deal with mutated virus variants. The novel platform-based vaccines have significantly reduced the lead time and time-to-market, which was proven during the COVID-19 pandemic by biopharmaceutical companies such as Pfizer/BioNTech and Moderna. With steps being undertaken to conduct quick trials, vaccines can be eventually deemed to be personalized and quick-build products. Finally, vaccine products are clearly highly process-intensive, where there are strict regulations in each step of the production process. This has led to issues related to controlling and measuring the state of the systems, which are to be addressed possibly by using analytical and/or data-driven mathematical models.

Moving forward, the production of the novel platform-based vaccines can be scaled up further by biopharmaceutical industries through a partnership with the different platform component producers and suppliers based on the changing requirements. Furthermore, virtual technology can be used to deliver real-time technical support and training between new and existing facilities, so that no compromise is made in safety, quality, and integrity. Seamless information exchange, which is one of the enablers of smart manufacturing, along with efficient technology transfer and global partnership, will help cut down research and development costs and efforts and make the process more flexible.

The research community has also started exploring the possibility of extending the novel platform idea to develop vaccines for diseases apart from COVID-19 such as influenza. If platform-based vaccine for influenza becomes a reality, it would be possible to develop these vaccines in a very short period, thus giving scientists a longer time frame to effectively identify the virus strains in the next flu season. As a result, the flu shots could be perfectly matched with the virus strains that are dominant in a particular season [45]. This can increase the efficacy of flu shots. Platform-based options are also being considered for creating personalized and customizable therapeutics to tackle diseases like cancer.

Additionally, the information about developing the vaccine platforms and modules could be documented for the possible creation of standards and roadmaps. These could be expanded and updated continuously to lay a strong foundation for interoperability and data exchange. Having such standards will not only reduce lead time, errors, and development and delivery costs but also will speed up the regulatory approval process. These standards could also be used to streamline vaccine manufacturing globally to guarantee quality and consistency in the production process, thereby conforming with Good Manufacturing Practices (GMP).

7 Disclaimer and Acknowledgment

Certain commercial systems, products, and applications identified in this paper are not intended to imply recommendation or endorsement by the National Institute of Standards and Technology, nor is it intended to imply that they are necessarily the best available for the purpose.

Conflict of Interest

There are no conflicts of interest.

Data Availability Statement

No data, models, or code were generated or used for this paper.

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