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# VACCINE INSIGHTS

## SPOTLIGHT ON:
## mRNA: harnessing the benefits, addressing the challenges

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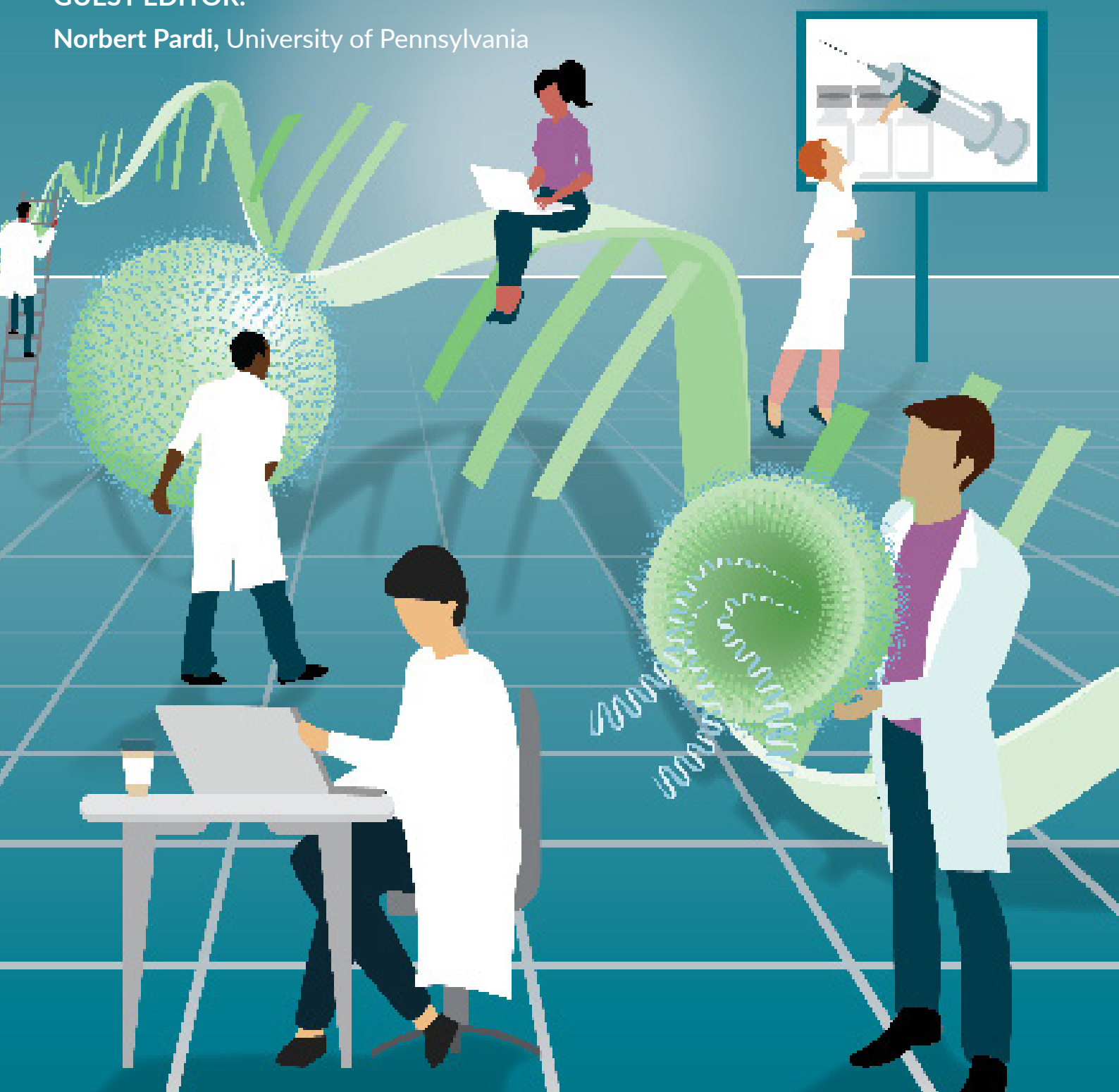

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VACCINEINSIGHTS

MRNA VACCINES: HARNESSING THE BENEFITS, ADDRESSING THE CHALLENGES

SPOTLIGHT

EXPERT INSIGHT

# A blueprint for quality by digital design to support rapid RNA vaccine process development, manufacturing & supply

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The COVID-19 crisis has highlighted the critical role of vaccine manufacturing in managing infectious disease outbreaks and pandemics. Enhancing RNA manufacturing capability, distribution and flexibility will now be central in future epidemic preparedness and emergency response strategies. This insight showcases the adaptation of Quality by Design (QbD) principles to RNA vaccine platform production processes. In particular, the implementation of a digital, holistic, and RNA-specific QbD approach can revolutionize vaccine development, regulatory approval, and manufacturing. We discuss how this framework can help overcome the remaining scientific, industrial, and regulatory challenges, potentially leading to a globally distributed network of versatile and pre-approved manufacturing platforms. A new blueprint is herein proposed for the development, validation and lifecycle management of these platform processes.

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## A PROMISING PLATFORM TECHNOLOGY FOR INFECTIOUS DISEASE MANAGEMENT

The rapid development of safe and efficient RNA-based vaccines against SARS-CoV2 has brought this new technology to the forefront of biotechnological innovations [1,2]. RNA manufacturing has played a critical role in vaccine supply and global vaccination programs, with new production processes being

developed and scaled up at unprecedented speeds [3].

The rapid vaccine development and production timelines, coupled with recent genotyping methods, make it particularly suitable to respond to emerging threats [4,5]. Vaccine design is highly versatile and enhanced by automated bioinformatic pipelines [6]. Within two days of the SARS-COV2 virus being sequenced, Moderna had designed its mRNA vaccines and had started phase I studies six weeks later with an initial clinical batch [7,8]. Furthermore, unlike conventional vaccines, RNA-based products can be developed and manufactured based on a potential disease-agnostic platform technology. Apart from the DNA template, the raw materials, consumables, equipment, staff, and analytical approaches can all remain unchanged across different vaccines [9]. Thus, production can be rapidly repurposed, and knowledge easily transferred. RNA manufacturing further relies on a small-scale, rapid, scalable, and affordable cell-free production system [4,10]. Compared to other emerging technology, RNA manufacturing appears relatively simple and transferable [11,12]. Overall, this already enabled the approval and mass production of life-saving vaccines in record time [13–15].

Although the efforts, collaborations, and flexibility seen during this health crisis deliver a hopeful message, the approach taken seems neither sustainable nor optimal to contain new emerging threats and manage infectious diseases. The high-risk financing strategy, unprecedented public incentives, and large-scale donations of vaccines are hardly applicable in the long run [16,17]. Additionally, production has rapidly gained pace but is currently highly centralized in high-income countries, while global demand is still not met [18]. Vaccine inequity notably contributed to many preventable deaths and economic damages in Low- and Middle-Income Countries (LMICs). Fair and global access to COVID-19 vaccines would also help to prevent the emergence of new variants worldwide. The disputes surrounding RNA vaccine allocations highlighted the need for LMICs to rapidly reach sovereignty over vaccine access [19]. It is now clear that strengthening domestic vaccine capacities in these countries is fundamental [20].

Moreover, the bright prospect of this technology is leading to increasing pressure for RNA platform development worldwide [21]. Currently, more than a hundred RNA vaccines are being developed against infectious diseases, with a pool of candidates in the clinical pipeline in exponential growth [22,23]. This list includes vaccines against many unmet medical needs, including malaria, HIV, and tuberculosis [24–26].

In addition, as of today, manufacturing processes have been mainly developed under a dominant Quality by Testing paradigm and scaled up in a relative emergency [3,27,28]. The requirements to transfer knowledge between vaccines and sites are not well-established yet. New manufacturing challenges are likely to emerge from multiproduct process development [29]. One of them will be the assurance of similar safety and quality level regardless of the RNA sequence, route of administration, and organ targeted [30–32]. Ensuring the thermostability of vaccines is also on everyone's mind [33,34]. On top of these industrial and scientific challenges, regulatory barriers still limit the versatility of RNA technology.

All of this illustrates the many gaps preventing this new technology from reaching its full potential. A truly immediate-response, multiproduct RNA platform is still not a reality today. The Global Pandemic Preparedness Summit's 100 Days Mission, aiming for access to safe and efficient vaccines within 100 days of outbreak identification, remains also a remote prospect [35]. However, an ambitious application of Quality by Design (QbD) principles appears very promising to underpin a paradigm shift [36,37]. QbD is defined as 'a systemic approach that emphasizes process control and product and process understanding based on sound science' [38]. In an enhanced framework, process knowledge is further supported by advanced analytics, modeling, and computational tools [39]. This


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initiative, strongly backed by regulators for many years, has been a step towards pharmaceutical continuous improvement, manufacturing modernization, and greater flexibility [40]. However, this powerful methodology has not yet been fully applied to a vaccine or any other platform technology [41].

## AN EVOLVING & NASCENT REGULATORY FRAMEWORK FOR RNA VACCINE RESPONSE

The COVID-19 pandemic shed light simultaneously on the regulatory path for vaccine emergency authorization and manufacturing process development [42,43]. Even during public-health crises, vaccine approval is highly regulated and monitored. Emergency use authorization (EUA) still requires detailed information on manufacturing and control [44]. More precisely, manufacturers need to demonstrate that production processes can consistently produce vaccines with adequate quality at commercial scale. Additional data can however be provided following initial approval, considering the patient risk-benefits balance, but without ever compromising on product safety and efficacy. Following ICH Q9 guidelines, product and process understanding can offer more flexibility on data requirements and post-approval commitments [45]. The extent of this remains determined by the application of adequate knowledge management and quality systems, aligned with the principles of ICH Q8 [46]. In the case of COVID-19 mRNA vaccines, it already led to a significant reduction in regulatory burden [27,28]. Amongst others, the European Medicines Agency (EMA), U.S. Food and Drug Association (FDA), and World Health Organization (WHO) have issued similar emergency use validation on this same basis [47].

However, many hurdles remain to streamlining and harmonizing such fast-track regulatory processes [48]. The exact requirements of EUA remain blurry, limiting fast decision-making and approval [49,50]. This is exacerbated by the high heterogeneity regarding approving, release testing, reviewing processes, and timelines worldwide [49,50]. Additionally, the lack of self-reliance and mutual recognition mechanisms between agencies compound the problem, undermining timely and sustainable access to vaccines. Global production of unified vaccines is further impeded by the fragmentation of this regulatory landscape. Thus, the challenge of providing a rapid and sustainable vaccine supply to affected populations, wherever they might be, requires thinking outside the box.

Notably, future guidance and approaches should embed the platform nature and the inherent specificities of RNA technology [51]. The current regulatory landscape for RNA remains nascent and incomplete [43,52]. Despite the full market authorization (FMA) of both Pfizer's and Moderna's vaccines against SARS-CoV-2, there is no consensus on manufacturing, control, and approval requirements [53,54].

Recently, the WHO launched consultations to draw up plans for convergence of industrial and regulatory practices for RNA vaccines evaluation [55]. Given the current state of knowledge, the initial draft guidance offers an open and flexible standard [56]. Crucially, the questions of knowledge transfer and RNA platform definition are explicitly addressed, raising hope for a seamless knowledge transfer between future vaccines. Now, practical and target guidance aiming at technology transfer and knowledge sharing would be welcomed for LMICs and would-be manufacturers.

Overall, while rapid development must remain fully compliant with global standards, there is still much room for innovation. Many proposals have already emerged to accelerate Chemistry Manufacturing and Control (CMC) vaccine development, further catalyzed by the COVID-19 crisis. Following Medicine Adaptive Pathways to Patients (MAPPs) CMC paper in 2017, the EMA and FDA set up the Joint Workshop and the Prior Knowledge Workshop [57,58]. These proposals tackle the use of prior

knowledge in accelerated regulatory applications, and a recent white paper from the European Federation of Pharmaceutical Industries and Associations (EFPIA) extended these principles toward COVID-19 vaccine development [59]. Numerous collaborations between key stakeholders have since been enhanced. It is concluded that the use of platform knowledge, science, and risk-based approaches are central to overcome current barriers and accelerate supply. Again, the implementation of a QbD framework, which is a global regulatory initiative, can play its full role [60]. Amongst others, it can help provide information outside of conventional approaches and represents a good trade-off between the lack of harmonization and the need for regulatory flexibility. Within this stringent regulatory landscape, QbD seems to offer many solutions throughout the RNA vaccine lifecycle, from initial platform development and pre-approval to manufacturing post-approval management.

## IMPLEMENTATION OF A HOLISTIC QUALITY BY DIGITAL DESIGN APPROACH TO RNA MANUFACTURING PLATFORM DEVELOPMENT

In its fullest form, QbD must be applied systematically throughout vaccine and process lifecycles [61]. QbD further culminates when this framework is used in combination with advanced analytical and modeling tools. We call this 'Quality by Digital Design (QbDD)' (Figure 1). From a platform perspective, the enhanced knowledge and control strategy can be transferred to new vaccines and processes.

[62][63]. The recent development of a disease-agnostic, RNA-specific framework provides initial guidance for rapid implementation [37]. In addition, the review of RNA vaccine critical quality attributes (CQAs), critical process parameters (CPPs) and product-process relationships offers an initial risk assessment to support this paradigm shift. The relative simplicity of vaccine design and production processes makes this technology perfectly suited for an early and ambitious QbDD implementation. Particularly, the cell-free nature of the In Vitro Transcription steps reduces the inherent variability of conventional cell-based upstream processes, facilitating knowledge transfer between vaccines. Similarly, the use of mechanistic models is particularly promising to optimize production processes and vaccines quality in a transferable manner [64].

More strikingly, for this manufacturing technology to achieve its platform potential, QbD appears as a canonical requirement. Recent knowledge assessments have highlighted the remaining unknowns and obstacles to achieving a versatile production platform [29,65,66]. Amongst others, it will be critical to better predict and control the impact of critical material attributes, RNA size, secondary structures, and plasmid DNA heterogeneities on process performance and product attributes [67]. In particular, it would unlock the development of promising, but more fragile, self-amplifying RNA vaccine technology [68,69]. Additionally, the manufacturing requirements for new routes of administration and organ-targeting strategies need to be resolved [70,71]. The ability to fine-tune the properties of RNA formulated in lipid nanoparticles (LNP), without jeopardizing RNA integrity or vaccine safety, seems crucial [72]. Ultimately, QbDD offers a path to overcome these scientific gaps, however, a switch from a product-centric towards a more platform-centric mindset looks necessary.

## OUTBREAK PREPAREDNESS: QBDD AS A KEY ENABLER OF PLATFORM PRE-APPROVAL

Following these principles, platform-specific regulatory approaches can be adopted to streamline, standardize and facilitate knowledge and data transfer. Within this scope, vaccines should be manufactured based on the same or highly similar manufacturing


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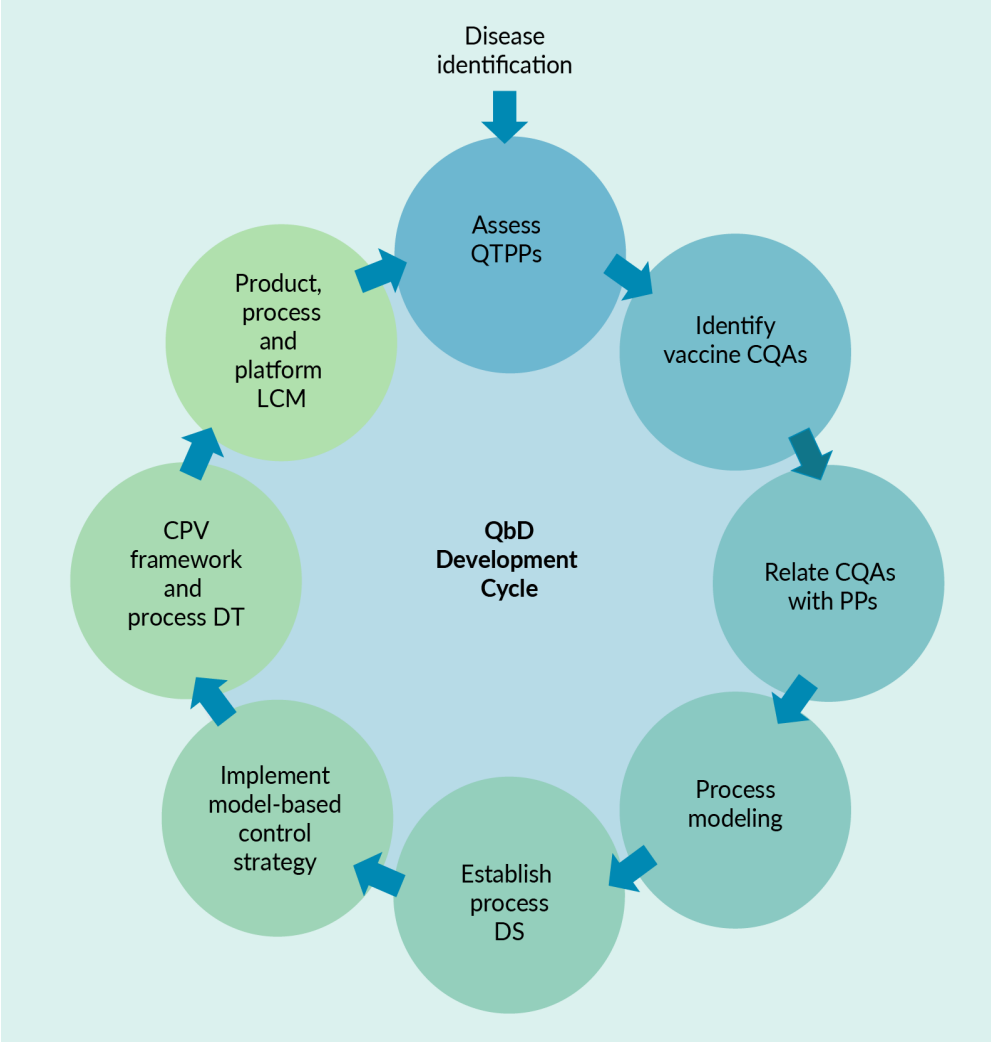
FIGURE 1

**QbDD continuous development principles.**




CPV: Continuous process verification; CQA: Critical quality attributes; DS: Design space; DT: Design twin; LCM: Life cycle management; PP: Process parameter; QbD: Quality by Design; QTPPs: quality target product profile.

process, refining the statutory definition of a 'platform'. The use of validated scale-down platform models to support such pre-approval also seems reasonable, given the scalability of current processes [59]. It should be noted that active substance (RNA) and drug product (RNA formulated in LNP) manufacturing can be decoupled if needed [49,50].

In this context, an RNA manufacturing platform can be pre-approved regardless of the precise RNA sequence and disease targeted. Platform data are thus required and should ideally include information from a wide spectrum of RNA vaccines. Prototypical libraries of RNA constructs and lipids can be established and updated in a risk-based manner. This will ultimately define an initial pre-approved scope for future vaccine development within the platform. In addition to conventional CQA testing, standardized protocols can be implemented to ensure production of consistent vaccines at different facilities. This could typically include in vitro potency assay and detailed measurement of RNA-LNP structure [73–75]. Exploring the limits of the Design Space can test the robustness and suitability of developed models. Additionally, the capability

of production processes can be thoroughly tested. For instance, the ability to tune immunogenic properties, LNP size, and surface charge can determine platform versatility [70,76,77]. Resolution criteria, such as size tuning at 10 nm intervals, can be proposed and defined [78].

Besides, a deep understanding of product-process interactions would be crucial to support this bold approach. Following QbD principles, a combination of prior knowledge, specific platform experiments, and risk assessments will help classify CQAs. Different subsets of CQAs will need to be accurately defined. For instance, product-specific and platform-specific CQAs can firstly be distinguished based on observed and predicted variability. Then, a more detailed review of the target ranges and controllability of vaccine specific CQAs can complete this assessment. As an example, while RNA integrity and LNP inner structure are likely to be vaccine- and sequence-dependent, advanced process control can limit the formation of certain product and process-related impurities in a completely disease-agnostic manner [79–81]. On the other hand, the therapeutic target is likely to define the desired LNP surface properties [82].

This leads to a re-thinking of conventional QbD regulatory tools. Process Design Space can be conceptualized in a more dynamic manner, with product-specific targets and properties as fundamental inputs. Some vaccine heterogeneities will necessitate further adaptation. A promising avenue is the use of hybrid modeling approaches, combining a mechanistic part, built primarily on platform data, and a vaccine-specific data-driven component [64]. The latter can cope with future vaccine heterogeneities, potentially relying on sequence data, plasmid DNA testing, or limited process data to adjust process operating regions. In time, machine learning methods will be able to extract key features of different therapeutic families. Another powerful tool to ensure consistent process and vaccine quality is the use of real-time model-based process control and digital twins [83]. As integral parts of vaccine process design and control, the principles of such modeling techniques can also belong to platform regulatory revisions.

Interestingly, this pre-approval could also encompass Good Manufacturing Practice (GMP) inspections, reviewing of quality and knowledge management systems. Quality control and assurance remain particularly critical in EUA filing. The application of QbD principles in analytical methods development, validation, and lifecycle management would therefore be essential [84]. In other words, the performance of analytics should remain suitable and consistent regardless of the RNA vaccine produced [85]. The newly drafted guidelines of ICH Q14 and Q2R2 should facilitate rapid industrial adaptation [86,87]. Additionally, the approval of an appropriate raw materials supply and testing strategy would also ease subsequent submissions [88].

Although platform pre-approval has not yet been implemented within the industry, this proposal remains fully compliant with current practices. From a regulatory perspective, it may be considered as an extension of current CMC rolling review principles to platform processes [89]. A redesigned lifecycle plan for process validation can be drawn from this (Figure 2). Regulators should however help manufacturers de-risk such platform development by providing vital guidance and assurances. A more formal acceptance of the 'platform' concept is awaited. The EMA already introduced the concept of a "platform technology master file" (PTMF), a comprehensive submitted dossier comprising all data and information relative to a platform [90]. While certified PTMFs are already in place for veterinary vaccines development, the Coalition for Epidemic Preparedness Innovations (CEPI) and International Alliance for Biological Standardization (IABS) are promoting its extension to human use as part of the revision of pharmaceutical legislation [91,92].

On a final note, pre-approved databases may take several forms, but need to remain flexible and upgradeable. Their scope is


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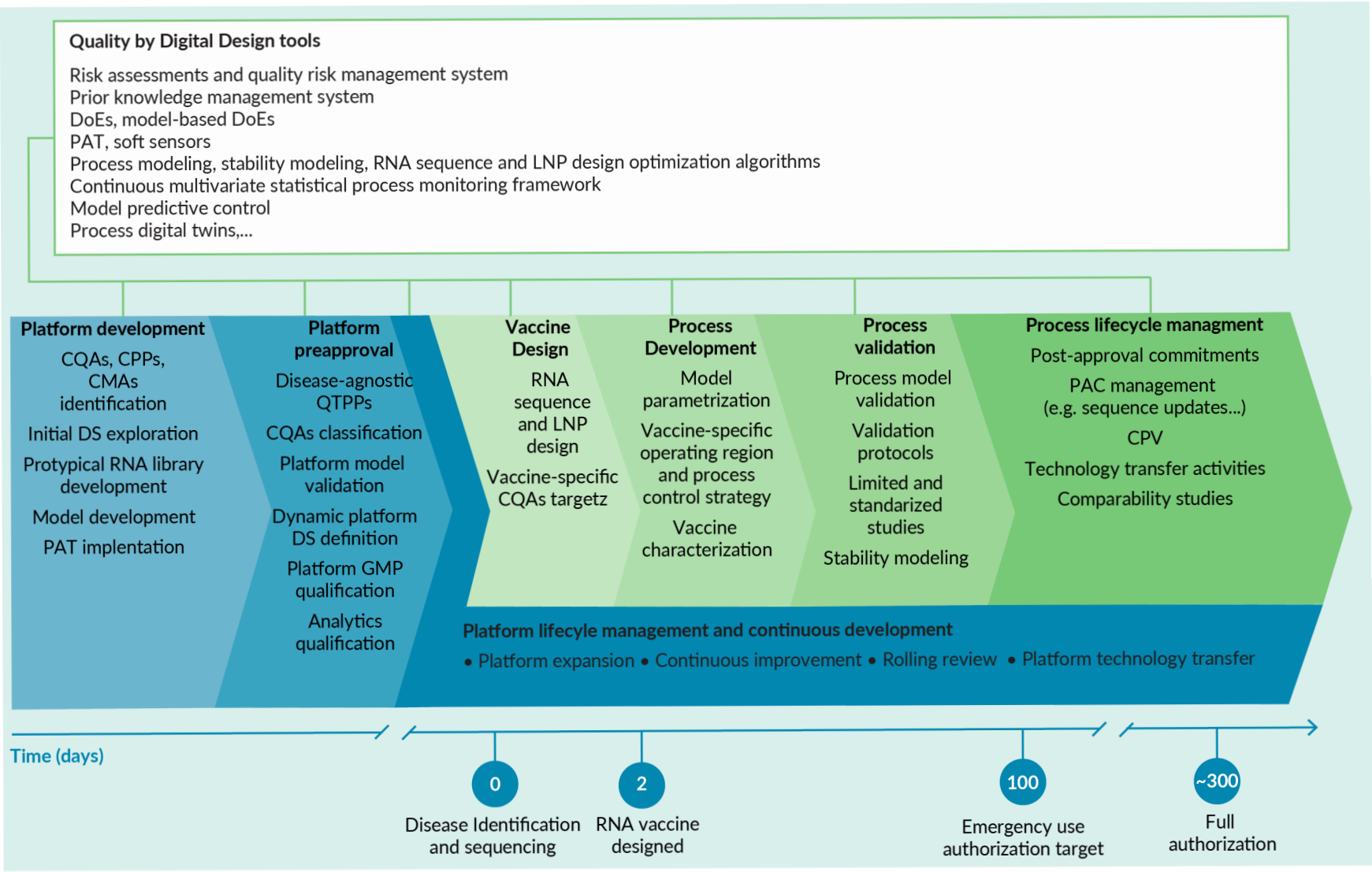
FIGURE 2

**Timelines of accelerated RNA vaccine development and response under an integrated QbDD framework.**




CMA: Critical material attribute; CPP: Critical process parameters; CPV: Continuous process verification; CQA: Critical quality attributes; DoEs: Design of Experiments;; DS: Design space, GMP: Good manufacturing practice; LNP: Lipid-based nanoparticle; PAC: Performance and availability cluster; PAT: process analytical technology; QTTPs: Quality Target Product profile.

likely to be determined by manufacturers' experience and investments, know-how sharing, and regulatory incentives. Besides, as a part of the platform lifecycle, each new vaccine developed under this scheme would contribute to updating and improving platform knowledge.

## OUTBREAK RESPONSE: QBDD-ASSISTED PROCESS DEVELOPMENT, VALIDATION & LIFECYCLE MANAGEMENT

Following the identification and genotyping of an emerging infectious disease, platform pre-approval can guide rapid process development and optimization. Even at the initial vaccine design stage, the QbD methodology is helpful. The gap between process and product development can indeed be bridged in the long run, although challenges will remain in identifying effective target antigens. For instance, sequence design strategies can include sequence manufacturability and their impact on other CQAs [93,94]. It would allow more consistent and optimal production, further ensuring CQAs and KPIs are likely to be met. Platform-specific sequence motifs could even be conceived [95,96].

At early process development, only a small subset of vaccine specific CQAs would now be scrutinized, limiting and streamlining the experimental work. The platform design space can thus be rapidly refined and restricted. Although entirely in silico process development can be possible in the future, other approaches include rapid parametrization of hybrid models and targeted testing at the plasmid or RNA levels. The measurement of RNA secondary structure, RNA-LNP structure, and thermal stability can be additional checks to set up vaccine-specific operating regions [97,98]. Model-based QbD can also greatly assist process scale-up and knowledge transfer. Both platform and process development could notably occur at validated small scale, further accelerating process design [59].

Once the manufacturing process has been optimized, the next critical step is process validation. Traditionally, this stage follows process development and scale-up. It is often rate-limiting in terms of regulatory approval, as process qualification requires full-scale vaccine-specific studies. An alternative and risk-based approach for EUA, relying extensively on a pre-approved RNA platform, is herein proposed.

First, process validation can take the form of limited studies and post-approval commitments, justified by rational platform knowledge. Ideally, standardized protocols, templates, and risk assessments can be drafted and made publicly available. These documents could detail minimum data requirements and studies, as well as good practices in the management and use of pre-approved platform databases. Besides, a holistic and digital QbD approach, supported by process analytical technologies (PAT), would enable the adoption of a robust continuous process verification (CPV) framework at manufacturing scale [99]. This will be of paramount importance in removing conventional testing and regulatory requirements.

Secondly, one of the major challenges of current RNA technology remains its thermal instability [100]. For example, approved mRNA vaccines against COVID-19 need to be stored below -20°C or lower and require complex cold chains for distribution and storage [101]. Although stability information is a requirement for shipping and approval, extensive core-shell data packages would certainly restrain urgent vaccine supply. While QbD can already be a key element in improving thermal stability, its potential is even greater [102]. Stability modeling can indeed be a powerful tool for predicting vaccine shelf-life [103]. Kinetic-based approaches have already been successfully implemented, and sequence-based algorithms are now under intense development to achieve vaccine-specific models [28,104,105]. Eventually, stability studies could be postponed post-approval.

Accelerated development also implies an increased number of pre- and post-approval manufacturing changes. Greater flexibility is therefore necessary to enable sustainable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supply while allowing continuous improvements. Briefly, it is crucial that changes can occur smoothly without additional clinical studies to demonstrate vaccine efficacy and safety. QbDD is once more essential to support risk-based comparability assessments [106]. Enhanced platform understanding and process modeling can together justify the preservations of many vaccine attributes and properties. Furthermore, an approved pharmaceutical quality system relying on model-based process control, PAT, and CPV can handle many changes routinely. Comparability demonstration can thus focus only on meaningful changes. These principles can be expanded towards variants management as, later, minor changes in RNA coding sequence can be considered as a moderate risk post-approval change. If supported by regulators, this could enable RNA technology to timely respond to emerging strains and variants [107]. Indeed, despite initial promises from manufacturers, the mRNA sequence of COVID-19 vaccines has not been yet updated to tackle the emergence of SARS-CoV2 variants [108].

In emergency situations, the scope of these comparability studies can go beyond continuous improvement activities. Similar templates and protocols can be applied to permit cross-platform production and the emergence of technology transfer hubs [109]. An assessment of manufacturing and analytical gaps will be required, but an alignment among stakeholders regarding testing and characterization studies could help streamline this process.

## TOWARDS A DISTRIBUTED MANUFACTURING LANDSCAPE

The RNA disruption process will certainly be fulfilled when these multiproduct production platforms are distributed worldwide. As stated above, international technology transfer is a requisite for global and equitable vaccine supplies. In the long term, the willingness of LMICs to produce their own vaccines is now evident. While Moderna is investing in Kenya, the WHO is launching a technology transfer hub in South Africa [110].

Even though many technical and industrial obstacles remain to be overcome in the near future, QbD will greatly assist such ambitious technology transfers [111]. First, the development of a science-based quality system is crucial, and likely rate-limiting, to entering the RNA field. QbD and process modeling enable new manufacturers to adjust to site-specific constraints and variabilities. The development of these standardized comparability studies would also be helpful. Additionally, the adoption of QbD and PAT would pave the way toward continuous manufacturing, further reducing costs, footprint, and financial resources required to set up new facilities. Simultaneous process digitization would also allow platform automation and limit the burden of quality control and the need for a highly skilled workforce. Research towards the development of such a small-scale, deployable, and automated platform is already underway [112,113]. Multiproduct manufacturing makes this approach even more economically attractive.

In summary, the proposed blueprint for future RNA development is driving a more localized manufacturing model, for the benefit of everyone. New RNA manufacturing sites can form the building blocks of a coordinated and agile manufacturing response to new infectious threats. This manufacturing network would allow regionalized response and vaccine campaigns, adapted to local needs. It will also ease clinical trial enrolments and foster innovations for unmet medical needs on a global scale. The development of robust and local supply chains would further foster flexibility and pandemic readiness. The on-site manufacturing of DNA under GMP guidelines, using for instance synthetic routes, could complement this decentralized manufacturing landscape [114]. Care will need to be taken with the management of the inbound materials supply chain for such a system, given the complex nature of some of the input materials (e.g., plasmid templates, enzymes, NTPs, and capping reagents) to ensure equivalent quality in different locales.

Learning from previous outbreaks, hesitancy and mistrust of this technology in LMICs can be reduced through the development of more local and trusted vaccine ecosystems. Partnerships and the formation of professionals need to be rapidly intensified. In addition, a network of infrastructure and logistics allowing mass vaccinations is needed in these countries. Oversight and regulatory mechanisms need to catch up in parallel.

## CONCLUSION

Given the stakes and the nature of RNA technology, the implementation of a holistic, digitized, and shared QbD framework is a realistic target. Its application goes beyond what we have seen and expected in other vaccine technologies. Firstly, it would enable truly disease-agnostic production processes, guarantying optimal quality and unlocking vaccine rationale design. QbD will also play a major role in accelerating vaccine process development and approval processes, while ensuring regulatory compliance and appropriate lifecycle management. This new blueprint still demands a profound restructuring of both manufacturing and approval processes and timelines. No shortcuts need to be taken, but continuous reviewing processes and platform development will be key. Finally, QbD can also be a cornerstone for international technology transfer. The successful implementation of these principles can eventually lead to a more distributed and agile manufacturing landscape. A reliable network of rapid-response, versatile and pre-approved platforms can be a great leap toward future outbreak containment and pandemic prevention. More than ever, coordinated efforts between RNA vaccine developers, manufacturers, states, and international bodies are needed.

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SPOTLIGHT

INTERVIEW

# RNA pioneer Ingmar Hoerr: from entrepreneur to philanthropist

**Charlotte Barker**, Editor, *BioInsights*, speaks to **Ingmar Hoerr,** co-founder of CureVac & Morpho Foundation


**INGMAR HOERR** founded "CureVac, the RNA people" together with colleagues in Tübingen, Germany in 2000. His entrepreneurship was motivated by his surprising discovery during his doctoral research that naked mRNA can be expressed in vivo without the risk of rapid degradation, while exhibiting the ability to generate strong specific immune responses, in contrast to what had previously been believed. During his time as CEO until June 2018, Ingmar initiated with CureVac the first clinical human trials testing mRNA therapeutics, thereby contributing to the development of the mRNA industry. During this time, he and his colleagues raised approximately $500 million in equity and significantly grew the company. He held the position of chair of the Supervisory Board of CureVac AG until March 2020. Ingmar was advisor to former EU commissioner Carlos Moedas of the European Innovation Council. He is a member of the Board of Trustees at the Max Planck Institute for Developmental Biology. In June 2021 he and his wife Sara Hoerr initiated the MORPHO Foundation, together with Florian von der Mülbe, also Founder of CureVac and his wife Kiriakoula Kapousouzi. He is Honorary Senator of the University of Tuebingen and in November 2021 he received the Honorary Citizenship of the City of Tuebingen.

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Ingmar Hoerr played a key role in the development of mRNA vaccines and therapeutics, co-founding CureVac in 2000. After suffering an aneurysm rupture in 2020, he left CureVac and found a new passion in the non-profit Morpho Foundation. We caught up with Hoerr to discuss his early work on RNA, life in a startup, and future hopes.

**Q** What was your route to working with RNA?

**IH:** It was my PhD at the University of Tübingen that got me started working in RNA. My mentor, Hans-Georg Rammensee, heard a talk in the US by Eli Gilboa, in which he described producing RNA-transfected dendritic cells and reinjecting them in mice to generate immune responses. We thought: why not just directly inject RNA into mice and see what happens?

I worked in collaboration with Günther Jung in the chemistry department, who was developing liposomes. I encapsulated RNA and plasmid DNA in these liposomes and also used naked RNA. I thought the naked RNA was too unstable and would be degraded within seconds when injected into mice but, to my astonishment, the naked RNA worked best, even better than the encapsulated RNA. I wanted to know how this RNA got into the cells so rapidly without being degraded. I immediately saw that it could be a great tool and felt compelled to continue this work. We now know RNA is much more stable than it was regarded at that time.

After my PhD, I interviewed for roles with pharmaceutical companies and told them about my RNA expertise, but they were completely uninterested in RNA. I could not follow my interest in RNA in the pharma business, so I was forced to do it alone.

**Q** Soon after your PhD, you co-founded CureVac – how did you approach launching a start-up?

**IH:** It felt like a big risk to launch a startup without any business expertise, so I did an MBA to help me get started with CureVac. Next, I worked to get some great scientists involved in the project. To garner the interest we needed, we knew we had to start clinical trials and gather human data.

What helped most was that I truly believed in the concept and had the data to back it up. It was the data that was driving things forward and helping me to achieve the goals I wanted.

**Q** How did you get funding for CureVac in those early days?

**IH:** We learned the hard way. We received a loan from the local bank in Tübingen to buy our first machines and pay the first employees. We persuaded the bank by

"...I truly believed in the concept and had the data to back it up. It was the data that was driving things forward and helping me to achieve the goals I wanted."


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explaining that we were also selling RNA to customers – a service business model was easier for them to understand.

To drive this service, we had to make a website and a catalog, arrange logistics, etc. We learned how to create a business from the very beginning – it was our sales that provided us with money to survive.

Later, we got access to an 'angel investor' and tried to secure funding via other venture capitalists. Unfortunately, our angel felt that the scientific community was not on our side, and we were forced to pay back his investment. We had a lot of problems raising money. We were not business people – we were scientists first and foremost – so fundraising did not always come naturally to us!

**Q** How does the unmodified RNA used by CureVac compare with the modified RNA now used in licensed mRNA vaccines?

**IH:** When we started CureVac, I knew nothing about modified RNA. I was using a natural stabilizing element found in Xenopus laevis – 5`and 3`untranslated regions at the ends of RNA, which exist for stabilization purposes rather than for translation.

In addition, we increased the GC content of the RNA to stabilize it, as GC has three hydrogen bonds, whilst AU has only two hydrogen bonds. This was our core technology from the beginning, and we obtained intellectual property protection for it.

Modified and unmodified approaches are not synergistic; you can use one or the other, but it is not possible to combine them. Therefore, we were hesitant to use Katalin Karikó's approach with modifications, because it would render our approach useless. CureVac has always focused on its own proprietary technology.

**Q** How do you feel about the success of RNA technology in COVID vaccines?

**IH:** I am very happy to see RNA emerging as a breakthrough technology, with many other companies now pursuing it and many new patents coming out. This is exactly what we wanted from the very beginning. I was always sad that there were only two or three companies out there working on this technology; it could have been much more.

Looking at what happened with COVID, RNA has proven that it has the potential to save the world. Without RNA, we may have found another solution, but not as quickly as we did with such a cost-saving method. It makes me very happy to see the proof of this technology.

RNA can be used in many applications, including vaccines, tumor therapy, and gene repair, and is always produced the same way. Coding on RNA is like a pencil writing on a piece of paper. I believe there is a bright future for RNA technologies in a range of diseases, for example, aging and malnutrition.

I left CureVac 2 years ago, due to health issues. However, I know the people currently working there are clever people who are driving the company forward. They are working to follow up with data, and I do not think they have any reason to stop now.

CureVac is going back to the cancer field, and I believe we can do a lot there. Cancer patients, who often do not have very strong immune systems, can be more tolerant of vaccines that provoke strong immune responses. It is possible that we will not see the side effects that we have seen with healthy people receiving RNA COVID vaccines.

"Together with my wife Sara and Florian von der Mülbe, Co-Founder of CureVac, and his wife, I founded the Morpho Foundation in Tübingen."

Finding people who believe in the technology can be hard, especially people with the money to make things happen. When talking to someone like Dietmar Hopp or Bill Gates, you can see their energy and enthusiasm for the cause. It makes me happy to have inspirational talks with these people who understand the potential of this technology and believe in change.

**Q** Looking back, is there anything you would have done differently?

**IH:** A lot of things, of course! Some things have to be learned the hard way. You must learn from mistakes – and try not to make the same mistake twice.

I am happy that we learned from misfortune and failures. For example, CureVac's prostate cancer vaccine did not work as we expected. Of course, we were sad, but we had to see how to adapt it so that it might work.

**Q** What is your main focus for the future?

**IH:** My current health issues have been the hardest thing I've faced in my life. Even harder than founding CureVac!

My family is now my priority – my wife and I have 7-year-old twin boys, and my family deserves more of my attention. Before my aneurysm, CureVac was my family. I was into CureVac with everything, body and soul. I needed to change that and have more real family time.

That said, I didn't want to just stay home – wanted to be involved in a start-up again. I find that the more people are around me and the more we talk about things, the less we actually achieve. I like to keep things simple, with a small team.

Together with my wife Sara and Florian von der Mülbe, Co-Founder of CureVac, and his wife, I founded the Morpho Foundation in Tübingen. We leverage our expertise in health and culture (my wife worked at the opera) to support a range of projects. For example, we are currently supporting projects related to medical care in India and theatre lessons in primary school.


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VACCINEINSIGHTS

RNA VACCINES: HARNESSING THE BENEFITS, ADDRESSING THE CHALLENGES

SPOTLIGHT

INNOVATOR INSIGHT

# Discovery to delivery in 100 days: RNA therapeutics & their role in future pandemic preparedness

Tracy Humphries

Recently, the Coalition Epidemic Preparedness Innovations (CEPI) announced their ambition to develop vaccines against emerging diseases in 100 days. mRNA vaccines are a manufacturing modality that is suited to meet the 100-day strategy. The technology offers great benefits and potential for infectious diseases and personalized medicines due to the advantages in flexibility, cost, and speed of development, but there are still challenges to overcome to fully realize the potential. How can manufacturers prepare for rapid response?

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## COVID-19 CHANGED THE VACCINE MANUFACTURING LANDSCAPE

The Covid-19 pandemic shone an intense spotlight on the vaccine industry, placing an unprecedented demand on biopharma manufacturers to develop and produce a vaccine in a severely shortened timeframe. Fortunately, what emerged were mRNA vaccines, which proved the potential of this type of nucleic acid–based therapeutic to be developed under a fast timeline while also showing high efficacy rates.

Following on from the lessons learnt during the pandemic, the Coalition for Epidemic Preparedness and Innovations (CEPI), hosted the Global Pandemic Preparedness Summit in collaboration with the UK Government. One of the key questions asked was

"What if it took 100 days to make a safe and effective vaccine against any virus?" Before the Covid-19 pandemic, a vaccine could take up to 10 years to develop, but this was condensed to just 326 days. Producing a vaccine in 100 days could save lives, decrease economic damage, and possibly even prevent outbreaks from becoming pandemics. It's an ambitious goal, but CEPI believe this is possible by tightening and shortening timelines at each stage [1].

Partnerships and collaborations were key to developing mRNA vaccines in a short time, and they will continue to be essential for the industry to achieve the 100-day timeline. While the coronavirus pandemic was a unique situation, it led to increased investment from governments, bilateral and multilateral donors, philanthropic organizations, development banks and private sector investors, into the vaccine industry and nucleic acid–based therapeutics overall [2]. With proven potential to treat diseases *in vivo* and offer long-lasting effects, nucleic acid–based therapies will continue to spark biopharma's creativity to develop more molecules with new functions to improve treatments and patient outcomes.

## ADVANCES IN NUCLEIC ACID-BASED THERAPEUTICS

There have been extraordinary leaps in advancing development of many types of therapeutics within the last decade, in part due to advances in genomics, such as in bioinformatics and sequencing. This includes the extraordinary achievement of mapping the human genome, unlocking molecular pathways important in disease [3].

Different modalities can be used to produce different types of therapeutics, for example, by using viral vectors, DNA, mRNA, and proteins. Different modalities will have different manufacturing challenges as well as different advantages and disadvantages, depending on what is needed by the manufacturer to produce the therapeutic of choice.

Viral vector systems are the traditional, well-established method for producing vaccines, with proven efficacy through clinical trials. There are many successful candidates in place and manufacturers have developed low-cost facilities around the technology. However, it is slower compared to other methods and requires the use of animal cells. It is generally suitable for mid- to large-batch scale. Protein vaccines also use the well-established methods of the growth of living organisms but can be relatively complex to manufacture.

Because of the disadvantages to using traditional methods, there is high demand for alternative vaccines with clinical efficacy, high design flexibility, and fast manufacturing timelines. Developing new nucleic acid–based therapeutics is a research area where this demand could be met.

> "Therapy with nucleic acids either uses unmodified DNA or RNA or closely related compounds. From both a development and regulatory perspective, they fall somewhere between small molecules and biologics. Several of these compounds are in clinical development and many have received regulatory approval for human use"
>
> - Sridharan and Gogtay, 2016 [4]

Nucleic acid–based therapeutics have particularly benefited from increased investment, collaboration, and partnerships, from the Covid-19 pandemic. Foreign Direct Investment (FDI) grew by 52% in 2021 according to GlobalData [5] with investments made to organizations providing services or products related to genomics, DNA and RNA sequencing and genetic engineering. Some examples of this increased activity are shown below:

- Merck announced a collaboration agreement with Orna Therapeutics a biotechnology company pioneering a new investigational class of engineered circular RNA (oRNA) therapies [6];


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- Eli Lilly have invested $ 700 million to create the Lilly Institute for Genetic Medicine, following their acquisition of Prevail Therapeutics, a gene therapy pioneer and investment into MiNA Therapeutics Ltd, a pioneer in RNA activation therapeutics [7,8];
- EtheRNA, a developer of mRNA therapeutics, has seen millions invested including from companies like Novalis [9];
- Arcturus, an mRNA medicines company, received $63.2 million from the US government to support development of saRNA vaccines [10].

With several start-ups now working in the early stage of next-generation RNA technologies, we should expect this interest to continue [11].

Nucleic acid–based therapeutics can be created using several sources. They include:

- DNA plasmids–small circular DNA molecule found in bacteria and other microscopic organisms that ranges in size from 4000–15000 base pairs;
- Protein-encoding mRNA–longer strand of mRNA, ranging from 100–20000 nucleotides, that is generally defined by the coding sequence it contains;
- Non-coding mRNA–shorter sequence of mRNA, ranging from 10–150 nucleotides, that does not contain a coding sequence (i.e., it is not translated into a protein)

## THE POTENTIAL OF RNA-BASED THERAPIES

There are different types of RNA, each with a unique function. A useful distinction is to broadly classify RNA molecules into coding RNA (e.g., mRNA) or non-coding RNA (ncRNA) (Figure 1). Self-amplifying RNA (saRNA), circular RNA (circRNA), and trans-amplifying RNA (taRNA) have been shown to have coding potential, but their functionality is largely uncharacterized. Less than 2% of the human genome sequences encode for proteins.

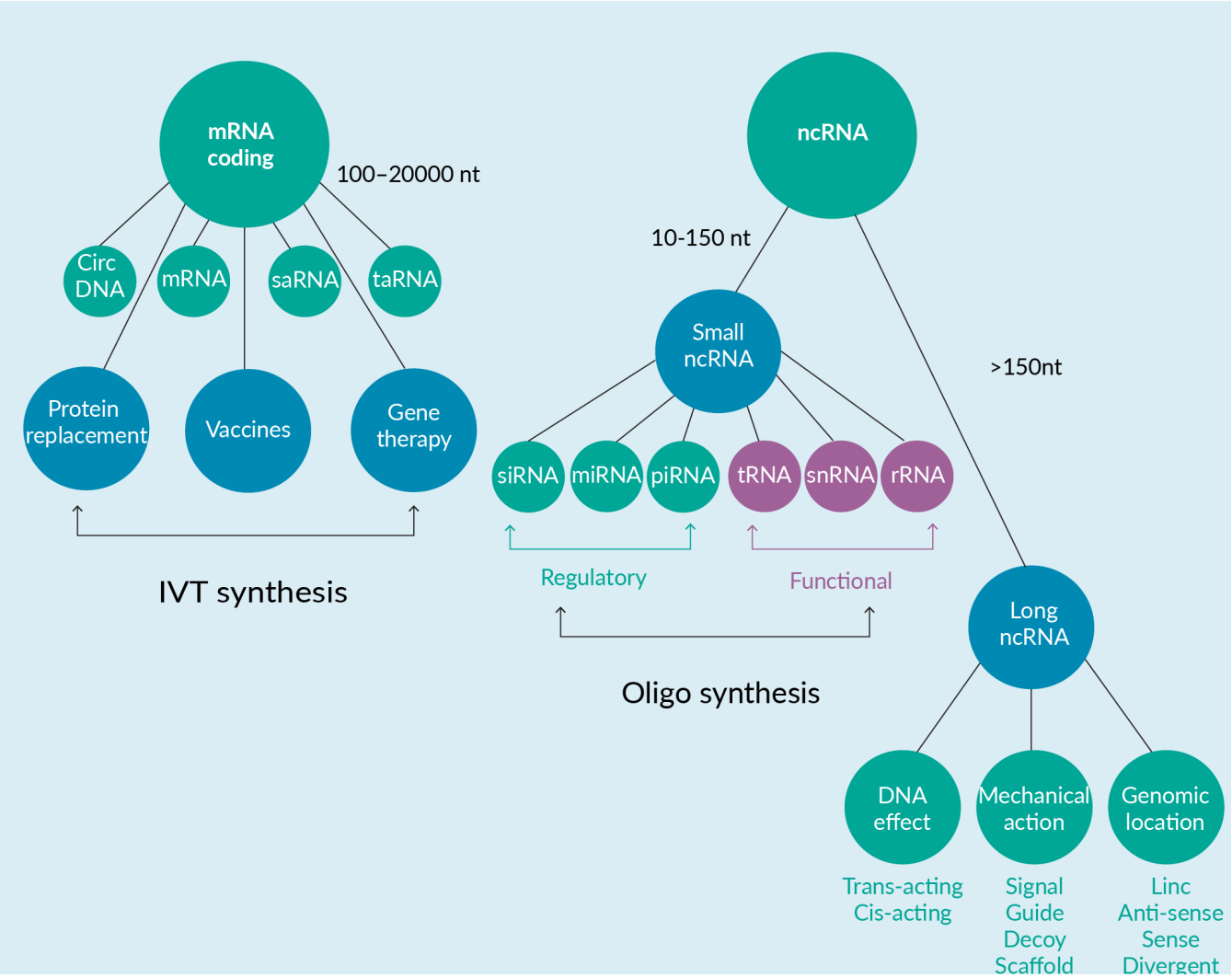
ncRNAs do not undergo translation, but they are believed to serve as regulatory elements in the genome. Thus, they could hold the key to broadening our understanding of gene regulation in the context of human disease. Examples of small ncRNAs include ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), piwi-interacting RNA (piRNA), micro-RNA (miRNA), and silencing RNA (siRNA).

This diversity provides huge potential but also brings interesting challenges for manufacturers, as it may be that different molecules are suitable for different therapeutics. For example, therapeutic modalities for mRNA include replacement therapy, vaccination, and cell therapy [16].Therapies created from siRNA usually involve gene down-regulation, miRNA target multiple genes within one pathway for broad but specific response, thus making them useful for cancer [17].

Most mRNA vaccines in clinical trials today are the traditional non-replicating type. Non-replicating mRNA vaccines are transient by nature and typically express antigen for a few hours or days. For some applications this can be beneficial; however, for others, such as systemic protein therapies, extended expression of a protein would be beneficial [18]. However, saRNA can deliver genes, such as a viral RNA polymerase, to enable mRNA to self-replicate. While this requires delivery of a more complex and longer RNA molecule, it could provide greatly enhanced biological activity, which allows for lower doses [19]. CircRNA is attractive for its increased stability, allowing rapid production via *in vitro* transcription without nucleotide modification, thus providing cost savings. However, at this time, it is still difficult to tell if it will offer more than linear mRNA. CircRNAs are expected to be potential biomarkers for many

## FIGURE 1

**Different types of coding mRNA and ncRNA molecules.**




RNA molecules classified into coding RNA (mRNA), where they carry the code for protein synthesis or non-coding. saRNA, circRNA and taRNA are shown here as having coding potential. ncRNAs do not undergo translation and there is a size different between the larger coding RNAs to the smaller ncRNAs. Examples of small ncRNAs include ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNAs (snRNA), piwi-interacting RNAs (piRNAs), micro RNAs (miRNA) and silencing RNA (siRNA). Some small ncRNAs are classed as having a regulatory effect and are involved in RNA silencing. miRNA modulates physiological and developmental gene expression. siRNA medicates sequence-specific cleavage of nascent mRNAs. piRNA may protect the germline from genome invaders [12]. Long ncRNAs (lncRNAs) are widely expressed and have key roles in gene regulation [13]. Categorization has been shown here based on action, but this is not exhaustive. mRNA can be in-vitro transcribed (IVT) for therapies [14] and for small ncRNA, oligo synthesis is an option [15].

diseases, with recent advances shown in melanoma [20].

## mRNA technology is changing the way therapies are developed

The potential of mRNA vaccines gained scientific attention in 1990 after the *in vivo* expression of a protein was observed upon injection of naked mRNA into the skeletal muscle of a mouse [21]. Since then, the industry has seen rapid development and expansion. Today, more than 140 clinical trials have looked at mRNA to address infectious disease, cancer, and a variety of other application areas.

While there are questions over the advantages and disadvantages of the types of mRNA, the overall potential is clear. mRNA therapeutics are currently being developed in many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areas. The advances made in mRNA vaccines for infectious diseases are renowned, but less is known about RNA therapies that are being developed by reimagining what is possible with existing technologies, such as *in vivo* gene editing techniques, RNA cell therapy as a safer alternative to CAR T and using mRNA to deliver the sequence of an antibody as an alternative to cells. RNA technologies are also being researched for use in allergen-specific immunotherapy [22] as well as in agriculture as a vehicle to replace pesticides [23].

mRNA systems in comparison to traditional viral vector systems, are much faster as they do not require animal cells. This also potentially makes them safer, although mRNA vaccines have yet to have the proven efficacy and safety of viral vector vaccines due to their novelty. Many manufacturers do not wish to invest in additional technology to manufacture a new modality, particularly one that currently has increased logistical costs. However, mRNA vaccines have the potential to work for small- to medium-batch sizes as well as large-batch scale, making them suitable for personalized medicine [24].

## NEW MODALITY FOR CANCER TREATMENT

mRNA vaccines have also gained traction as a therapeutic approach for treating cancer. mRNA can elicit immune responses to mutated oncogenes or regulatory cancer genes such as TP53, which are shared across many cancers, in a therapeutic pan-cancer approach. Other approaches for cancer include personalized therapy, where vaccines are developed for a person's individual mutations. In this regard, a patient's mutanome would be identified by next-generation sequencing, and a handful of custom mRNA vaccines would be developed targeting the individual's neoantigens [25].

The speed and potential cost gains of mRNA technology make it an interesting technology for personalized medicine. It is possible to take tumor tissue samples and develop mRNA vaccines that result in the expression of tumor antigens [26]. Many companies are working on integrated system mRNA processing solutions for this, such as CureVac with an mRNA printer and companies pursuing plug and play approaches like Nutcracker Therapeutics [24]. However, there is also room for improvement in smaller scale cGMP manufacturing, as much of the current equipment is repurposed from the biotech industry and is designed for much larger scales than needed for mRNA.

Therapeutic cancer vaccines are advancing quickly in development, with over 70 clinical trials completed and more results expected in the next two to three years [21]. Techniques under evaluation include the direct stimulation of antigen-presenting cells via *ex vivo* electroporation of mRNA. Other approaches include direct intratumor injection, whole body approaches, and targeted organ approaches. Currently over 50% of clinical trials using mRNA focus on the treatment of melanomas and prostate and brain cancer [21]. Thus, while numerous applications of mRNA vaccines are in various stages of development, targeting specific organs, tissues, and cells with lipid nanoparticles (LNPs) is still under research.

## CONSIDERATIONS FOR RAPID PANDEMIC RESPONSE

In an article for The New England Journal of Medicine [27], several doctors and scientists who work at CEPI wrote that there are five categories to focus on to enable a rapid vaccine strategy:

- Leveraging insights about new pathogens and technologies;
- Supporting innovation in the vaccine development process;
- Advancing analytics to inform processes;
- Promoting collaboration among stakeholders;
- Continuously reviewing evidence to support approval

Implementing current best practices while leveraging these goals could enable developing pandemic vaccines in 100 days. To allow rapid testing of candidates, the National Institute of Allergy, and Infectious Diseases (NIAID) proposed to develop and characterize prototype vaccines [28,29]. The goals for the NIAID Preparedness Plan are similar in scope, proposing to [30]:

- Characterize pathogens of concern;
- Shorten timelines between pathogen emergence and countermeasures;
- Bridge or eliminate gaps in research, infrastructure, and technology

Key findings from previous pandemics and epidemics indicate a lack of existing diagnostics, therapeutics, and vaccines, low manufacturing capacity; process efficiencies, and a lack of coordination and preparedness [31]. The 100-day mission suggests that embedding best practices and preparation into usual process measures is needed, for example, by making simplified and transferable manufacturing practices the norm and enabling scaled-up processes when needed.

With several choices available, it may be that manufacturers of therapeutics will need to adopt a flexible approach to manufacturing, as one modality could suit a specific therapeutic better than another. At this time, manufacturers may find themselves with a choice to stay with a specific modality (e.g., mRNA vaccines, viral vector vaccines) or focus on a specific research area and adapt manufacturing to what is needed. This requires a degree of resilience in manufacturing strategies.

The timeline for manufacturing and release of a clinical-grade vaccine will always be platform dependent, but mRNA vaccines offer the potential to be completed in as little as five weeks [27], in comparison to viral vector systems which can take around 6–36 months [21]. The increased speed from discovery to delivery for mRNA vaccines, will enable manufacturers to bring vaccines to the market quicker. This allows the technology to be suitable for meeting the 100-day strategy timeline. However, to be able to achieve this, manufacturers need to enhance their platforms now for rapid scale-up potential.

## OVERCOMING MANUFACTURING CHALLENGES

While there are many challenges to manufacturing a therapeutic, a key challenge is adapting processes. Often, solutions are home-built or optimized for other molecules and distributed processes can lead to bottlenecks. Many manufacturers don't have as much knowledge of these new arenas of manufacturing development and so they have not yet been standardized. This leads to challenges with operations, personnel, process, quality control, contamination, and others.

Process is central to biomanufacturing. A biomanufacturing enterprise includes processing parameters, facility, resources, and infrastructure; these elements are integrated and influence each other. When assessing vaccine manufacturing, many of the technical operations will be translatable, regardless of modality, especially when following GMP manufacturing guidance. While some processes will be different for each modality, there will also be many similarities in operations, such as the equipment used for purification and *in vitro* transcription (IVT). Holistic solutions can reduce project risks, stabilize costs, maximize capacity, and help speed up time to market.

One challenge for mRNA manufacturing is that it is much smaller scale than traditional cell-based modality manufacturing, requiring manufacturers to think differently about their space. However, this is one of the reasons why mRNA is so attractive, as it can provide considerable space and cost savings. Changing parameters in cell-based manufacturing usually results in time delays, whereas in mRNA manufacturing this is much quicker and doesn't have as many contamination issues to address. This makes mRNA vaccines suitable for the 100-day strategy.


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Process challenges for mRNA include DNA linearization and purity at various stages of the process. Purification can be more challenging for mRNA molecules because, due to their size and varying impurity profiles, they do not interact well with traditional chromatography resins. Flexibility in purification technologies or allowing process development scientists to mix and match media based on the specific characteristics the molecule, may help alleviate this problem. Other challenges can include obtaining GMP-grade reagents and ensuring continuous supply of raw materials.

## FLEXIBILITY TO SCALE IS KEY TO SUCCESS

With more modality and scale diversity than ever before, it's important to build in flexible and resilient solutions that allow researchers the ability to scale, and scale rapidly, if needed. One of the most common bottlenecks in the current manufacturing of mRNA is scaling, with mass population vaccines needing larger-scale production technology. Manufacturers can build flexibility into their processes by ensuring that equipment is scalable and supports the transfer from process development to GMP manufacturing. Flexible, configurable manufacturing solutions, such as the Cytiva FlexFactory™ platform and KUBio™ modular facilities, offer full start-to-finish, tailored solutions, developed and delivered for monoclonal antibody (mAb) applications as well as for plasmids, mRNA, and viral vectors.

One way to look at the scale of manufacturing is to estimate market size, the uptake of a potential therapy, and the dosing strategy, and then back calculate from that. Investing in flexibility will make it possible to grow, allowing a small fast start with something that is easy to scale up or scale out. Considering manufacturability and scale-up from the beginning can avoid problems later in the process. A protocol or method that quickly gives a pure product for early clinical material might be great, but if it can't scale up or be used in manufacturing, this will become an issue.

Manufacturability includes assessing material suitability and thinking about material sourcing early. Continuous planning, including maintaining a close relationship and regular communication with suppliers, is critical for rapid expansion of manufacturing facilities. It is also essential to know the quality attributes of the product, so early thinking on QC testing can save time later in the process.

Targeted delivery of mRNA therapeutics is an issue that needs to be addressed, as mRNA is unstable and needs protection from RNAse degradation. Delivery methods include lipid-based nanoparticles (LNPs), polymer nanomaterials, silica nanoparticles, carbon and gold nanomaterials and N-Acetylgalactosamine (GalNAc). Examples of proven efficacy of the LNP platform include patisirin and Alnylam and the COVID-19 vaccine from BioNTech and Moderna [16].

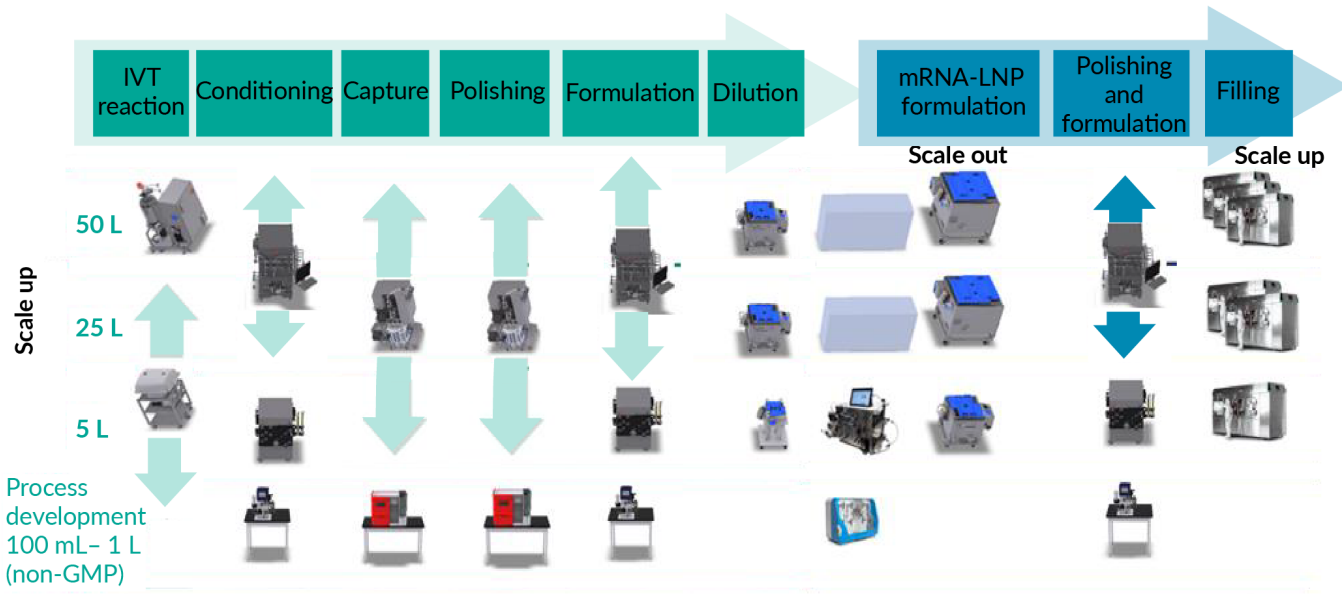
LNPs are typically formed in a rapid mixing process using microfluidic devices [32], which is more of an art than an established method. Greater understanding of the influences of the LNP ingredients and their effect on LNP stability, delivery, efficiency, immune response, and ultimately patient outcomes would benefit the industry [32]. Optimization of LNPs and other delivery technologies is critical to determining the ultimate success or failure of a therapeutic.

Filling and finishing of vaccines will also need to be considered for rapid response. Distribution can be an issue, as current mRNA vaccines require frozen storage. Alternative methods, such as lyophilization, are under study [33], with Gennova recently achieving approval for its COVID-19 vaccine in powder form [34].

The ethos of flexible and scalable solutions is something that Cytiva promotes across many product ranges, allowing support of manufacturing in various modalities, including non-viral delivery for genomic medicines, and at different scales (Figure 2). Manufacturers can be prepared for future pandemics by

## FIGURE 2

**Scalable equipment, from process development to manufacturing and flexible single-use components, support optimization.**




Scalable equipment from process development to manufacturing and flexible single-use components supports optimization.

building flexibility into their processes, helping to ensure that equipment is scalable and supports the transfer from process development to GMP manufacturing at a rapid pace.

## RNA TECHNOLOGY & THE POTENTIAL OF THE 100-DAY VACCINE

Currently, mRNA vaccines are one of the most suitable manufacturing modalities to meet the 100-day vaccine strategy, due to the increased speed they offer during the manufacturing stage. RNA therapeutics is a rapidly growing field, with many applications in development and therapeutics in clinical trials. The technology offers great potential in the areas of infectious disease and personalized medicine due to its advantages in flexibility, cost, and speed of development. There are still challenges to overcome to fully realize the possibilities, but some of these will be addressed with increased focus and funding.

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VACCINEINSIGHTS

MRNA VACCINES: HARNESSING THE BENEFITS, ADDRESSING THE CHALLENGES

SPOTLIGHT

COMMENTARY

# mRNA Vaccines: a growing and complex IP landscape

Robert Burrows & Ellen Lambrix

The success of mRNA vaccines against COVID-19 has fueled significant global interest in the development of mRNA vaccines against other infectious diseases and cancer. The COVID-19 pandemic has also highlighted the complex and fragmented nature of the intellectual property landscape relating to mRNA vaccines. 2022 has also seen the first significant patent infringement cases relating to mRNA vaccines. This article examines the types of patents that protect key aspects of mRNA vaccine technology and considers the impact of the existing IP landscape and recent patent litigation on future mRNA vaccine development.

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## INTRODUCTION

It has been less than 2 years since the first messenger RNA (mRNA) based vaccines were approved for use against coronavirus disease (COVID-19), yet in that short time billions of doses of those mRNA vaccines have been administered globally and millions of lives have been saved as a result. This success has fueled significant global interest in the development of mRNA vaccines against other infectious diseases and cancer. Numerous companies and institutions are actively carrying out research into mRNA vaccines and a number of mRNA vaccines for indications other than COVID-19 are now being tested in the clinic. However, although the first mRNA-based vaccines have only recently been approved for use, the mRNA vaccine platforms used and under development today are underpinned by a multi-decade-long history of research and development.

As well as shining a spotlight on mRNA vaccines as a new and promising category of vaccines, the COVID-19 pandemic has also

generated significant interest in intellectual property and debate about the role that patents play in enabling or hindering innovation. This scrutiny has also highlighted the complexity of the intellectual property landscape relating to mRNA vaccines. Perhaps unsurprisingly, the number of patent applications filed relating to the use of mRNA as a vaccine for both infectious diseases and cancer increased dramatically over the five years to 2020 with patent owners ranging from large multinational biopharma companies and smaller biotech companies to universities and research institutions [1]. Given the long history of development, the platform nature of mRNA vaccine technology, and the growing number of entities conducting research in the field, it will also come as no surprise that the intellectual property landscape relating to mRNA vaccines is complex and highly fragmented.

2022 has seen the first significant patent infringement cases relating to mRNA vaccines. These high-profile cases illustrate how important it will be for anyone developing new mRNA vaccines to appreciate the complex patent landscape surrounding mRNA vaccines and the resultant need to consider intellectual property strategy and freedom to operate issues early in development.

In this article, we examine the types of patent that protect key aspects of mRNA vaccine technology. We also consider recent patent litigation and the impact of the existing intellectual property (IP) landscape on future vaccine development. This article is based on publicly available information only, is non-exhaustive, and is not intended as legal advice.

## PATENTS: A BRIEF INTRODUCTION

A granted patent provides its owner (or possibly its licensee) with the right to prevent others from exploiting the invention claimed by the patent for a limited period. In the UK and the US and many other jurisdictions, the term of a patent is 20 years from the date of filing, although patent term extensions can be obtained in certain countries; such extensions, which can be up to an additional 5 years in the UK and the US, are designed to compensate the patent holder for delays to market that are caused by the regulatory approval processes for new medicinal products.

Patents are territorial, which means that a patent can only be used to prevent infringing activities in the country in which it is granted. Patent portfolios, therefore, consist of a series of national patents each covering a different jurisdiction. While some patent owners may take a global approach to patent filing, often the costs associated with filing and maintaining patents mean that patent owners will focus geographic coverage on key jurisdictions (which may vary from product to product).

The inventions protected by patents can be broadly categorized as products or processes. However, there are multiple different claim types that can be granted, and which set out the boundaries of the protected invention. With regard to mRNA vaccines, and by way of example, such claims could cover the mRNA sequence itself, the delivery system for the mRNA vaccine, the dosage regimen for the mRNA vaccine, the medical use(s) for the mRNA vaccine, processes for producing mRNA vaccines generally, and processes for the manufacture of a particular mRNA vaccine.

Although the focus of this article is on patents, it is important to appreciate that patents are not the only means by which innovations can be protected. An alternative is to rely on confidentiality restrictions and trade secrets law to protect unpatented know-how. This can be particularly useful in protecting aspects of a product, its development, or manufacture which may be difficult to obtain a patent for (such as drug discovery and development methods).

## MRNA VACCINES & PLATFORM DEVELOPMENT

One of the reasons why mRNA vaccines have generated so much attention is the platform


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nature of the technology. mRNA vaccines have been described as 'plug and play'; a reference to the fact that, in theory, only the mRNA coding region need be changed in order for an mRNA vaccine to target a different indication. From a public health perspective, this is attractive because it could enable new vaccines to be developed rapidly in response to new viral threats and updated quickly to address new variants. From a commercial perspective, an mRNA vaccine platform could accelerate time spent in early development and enable more standardized large-scale production. The platform nature of mRNA technology also means that mRNA could potentially be used as a vaccine for a wide range of diseases. Illustrating this versatility, a number of mRNA vaccines for indications other than COVID-19 are now being tested in the clinic, including vaccines against Cytomegalovirus, Respiratory syncytial virus, Human immunodeficiency virus, and different cancer types including melanoma and colorectal cancer [2].

Despite the headline-grabbing stories detailing the astonishingly rapid development of both the Moderna and Pfizer/BioNTech COVID-19 vaccines, the two vaccines are in fact underpinned by decades of development work into both mRNA and delivery platforms. Importantly, from an intellectual property perspective, this means that a number of patents relevant to mRNA vaccine platforms pre-date the COVID-19 pandemic.

mRNA was discovered in 1961[3] and the possibility of harnessing mRNA as a drug or a vaccine has long been considered. However, it wasn't until the 1990s that research on mRNA began to gain momentum, and even then, the field of synthetic mRNA research encountered many challenges. Challenges that researchers developing mRNA vaccine platforms have needed to overcome include ensuring that mRNA does not trigger an adverse immune response, that the mRNA can be delivered into host cells without being degraded, that the mRNA can be correctly read by ribosomes inside a patient's cells, and that host cells express enough of the encoded antigen to have a therapeutic effect. As the field has progressed, researchers have found solutions to each of these challenges, and interest in mRNA vaccines has grown. In recent years, companies active in the mRNA field have been investing heavily in designing and optimizing their mRNA platforms to address each of these challenges. This has translated into a significant focus on, and patenting of, mRNA sequence engineering and chemistry, delivery systems (including composition and chemistry of lipid nanoparticle delivery systems) and manufacturing processes.

## Nucleoside-modified mRNA

One of the key breakthroughs in the field of mRNA came in 2005, when discoveries made by Katalin Karikó and Drew Weissman at the University of Pennsylvania solved the issue of synthetic mRNA triggering an uncontrolled immune response in patients [4]. Kariko and Weissman discovered that by incorporating pseudouridine (a naturally modified mRNA nucleoside), instead of uridine, the modified mRNA could circumvent the body's inflammatory immune response to the synthetic mRNA [5]. The University of Pennsylvania, therefore, owns a number of patents relating to nucleoside-modified mRNAs and their uses. Both Moderna and Pfizer/BioNTech's COVID-19 vaccines use a modified nucleoside approach and, according to securities and exchange commission (SEC) filings, both companies have taken non-exclusive sub-licenses of mRNA patents owned by the University of Pennsylvania (via a cascade of sub-licenses from mRNA RiboTherapeutics and Cellscript). Whilst these licenses are non-exclusive, SEC filings indicate that mRNA RiboTherapeutics and Cellscript are subject to certain time restrictions on granting additional sublicenses for *in vivo* uses in humans.

While not all mRNA vaccines under development have used the same nucleoside-modified approach, disappointing trial results from CureVac's first generation

mRNA COVID-19 vaccine, which used normal uridine instead of pseudouridine, led to speculation that it was this difference which resulted in lower-than-hoped-for efficacy compared to the Moderna and Pfizer/BioNTech vaccines [6].While it is too early to know for sure, the success of the Moderna and Pfizer/BioNTech COVID-19 vaccines seems to support the case for modified mRNA, and in turn the value of the patents owned by the University of Pennsylvania (licensed to mRNA RiboTherapeutics and Cellscript).

## Delivery, delivery, delivery - LNP composition and chemistry

mRNA is inherently unstable [7] and to function *in vivo* needs to be packaged inside a delivery system to ensure that it can be safely delivered into target cells without being degraded. Delivery has long been recognized as one of the key obstacles to the successful development of RNA-based technologies; as Nobel Prize-winning researcher and Alnylam co-founder, Phillip Sharp, was quoted as saying as early as 2003, the major hurdle for RNA is "delivery, delivery, delivery" [8].

Lipid nanoparticles (LNPs), used to encapsulate mRNA, are currently the most commonly used delivery system for mRNA vaccines [9]. Although other delivery systems have been developed (including lipids, lipid-like materials, polymers, and protein derivatives) [10], LNPs are currently the only delivery technology that is approved for use in mRNA vaccines (used by both the Pfizer/BioNTech and Moderna COVID-19 vaccines).

Like mRNA, LNPs also have a long history of development. Early work on LNPs was carried out by Pieter Cullis and his laboratory at the University of British Columbia and LNP technology was further developed by a number of companies associated with Cullis, including Canadian biotech companies Arbutus Biopharma Corporation (Arbutus) and Acuitas Therapeutics, Inc. (Acuitas) [11,12]. Several companies have since taken licenses of LNP patents from Arbutus and, in 2018, Arbutus spun out rights to its LNP technology (excluding rights to hepatitis B) into Genevant Sciences GmBH (Genevant) as part of a joint venture with Roivant Sciences Ltd.

Prior to the development of the mRNA COVID-19 vaccines, LNPs had already been successfully used as a delivery system for other technologies, most notably in RNAi therapeutics pioneered by Alnylam Pharmaceuticals (Alnylam) and also recently in genome editing technology. Alnylam gained approval in 2018 for the world's first approved RNAi therapeutic, ONPATTRO (patisiran), which is currently approved for the treatment of polyneuropathy caused by hereditary ATTR amyloidosis. ONPATTRO uses an LNP system that was developed by Arbutus and in-licensed by Alnylam. Alnylam itself has also developed its own proprietary LNP systems and owns several patents covering novel cationic biodegradable lipids. Patents owned by Arbutus and Alnylam have each been the subject of recent patent litigation relating to COVID-19 vaccines (discussed further below).

The LNPs used in the mRNA COVID-19 vaccines consist of four main components: a neutral phospholipid, cholesterol, a polyethylene-glycol (PEG)-lipid, and an ionizable cationic lipid [13]. Each element of an LNP affects the properties and function of an LNP system and there is, therefore, significant scope for engineering and optimizing LNPs. With research ongoing to address remaining challenges associated with LNPs (such as shelf-life and stability, targeting, optimal loading, and manufacturing challenges) [14] it seems likely that the number of patents relating to the use of LNPs in the delivery of mRNA vaccines will continue to grow. Companies involved in the development of mRNA vaccines (including Moderna and BioNTech) have been investing significant time and efforts into optimizing the chemistry and safety of LNPs and developing their own proprietary systems. SEC filings from Moderna indicate that it has an extensive portfolio of patents relating to its mRNA platform,


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including novel lipid components designed for optimal expression of both therapeutic and vaccine mRNAs.

BioNTech uses a number of delivery formulations for its products, including lipid nanoparticles and its own proprietary lipoplex (lipid carriers) formulations for which it has several patent filings in its sole name. Again, reflecting the importance of delivery systems to the success of an mRNA product, SEC filings reveal that BioNTech also has several active third-party partnerships focused on this area including a non-exclusive license from Acuitas for LNP formulations used in the Pfizer/BioNTech COVID-19 vaccine.

## MRNA VACCINE PATENT PORTFOLIOS

Aside from patents covering nucleoside modification and delivery technology, there are a variety of other types of patent which may cover an mRNA vaccine candidate. These include mRNA vaccine compositions encoding antigens for specific indications, mRNA sequence engineering and chemistry (including patents directed at various features of mRNA structure), engineered protein sequence patents, and patents covering different aspects of mRNA manufacturing.

According to SEC Filings, as of December 31 2021, Moderna had more than 170 issued or allowed U.S. patents or patent applications, more than 110 granted or allowed patents in jurisdictions outside of the US, and over 430 additional pending patent applications. Moderna's SEC filings state that the company typically pursues patent protection for both product and method of use claims. Moderna has a broad prophylactic vaccine patent family including claims to lipid nanoparticle encapsulated mRNAs that encode infectious disease antigens for different indications (including COVID-19) and also includes methods using those compositions for vaccination.

BioNTech has also indicated it has a broad patent estate comprising over 100 patent families owned by BioNTech (exclusively or jointly), all of which include at least one filing in the EU or US with several pending or granted patents in multiple jurisdictions. BioNTech's SEC filings suggest that its patent estate includes patents directed to features of therapeutic mRNA structures, mRNA formulations (including its lipoplex formulations and lipid nanoparticles), mRNA manufacturing, and uses of mRNA therapeutics.

Aside from Moderna and BioNTech, there are also many other companies actively developing mRNA vaccines including CureVac, GlaxoSmithKline, Sanofi (having acquired Translate Bio in 2021), and Arcturus Therapeutics, each of which is also building patent portfolios relating to mRNA vaccines.

## PATENTING CHALLENGES

Although precise requirements vary from jurisdiction to jurisdiction, as a minimum, a patent will only be granted for new and inventive products or processes. This generally means that the claimed invention cannot have been published previously. In addition, the invention cannot be an obvious iteration of something that existed beforehand. In the context of an mRNA vaccine, these requirements for novelty and non-obviousness present certain challenges to patentability. For example, if the sequence of the antigen or protein encoded by the mRNA has been published, then the coding region of the mRNA is unlikely to be patentable. Even if the translated protein has been engineered, it may still be difficult to obtain a patent for the related mRNA coding region if the steps taken to engineer the relevant antigen or protein were obvious.

Interestingly, despite the commercial success of both the Moderna and Pfizer/BioNTech COVID-19 vaccines, early patent applications filed for both vaccines are facing considerable uncertainty as to whether they will proceed to grant. International Search Reports prepared by the European Patent Office (EPO) have highlighted issues with both novelty and inventive step based on the prior

publication of the SARS-CoV-2 genome and prior publications which described specific proline substitutions (so-called 2P mutations) which had previously been made to other coronaviruses (and for which the US National Institutes of Health (NIH) has been granted a patent) [15].

These patentability challenges associated with claims for mRNA vaccines encoding previously published proteins, or proteins that have been engineered in a previously published manner, mean that some of the other types of patents relating to mRNA vaccines highlighted above (such as LNP chemistry and formulation and manufacturing patents) may become more valuable.

## PATENT LITIGATION: THE START OF AN LNP PATENT WAR?

Given the number of companies active in this space and the potential commercial value of the resulting mRNA vaccines and associated technology, patent litigation in the field has seemed inevitable. This year a number of patent infringement cases relating to the Moderna and Pfizer/BioNTech COVID-19 mRNA vaccines have been reported in the UK press and specialist biotech publications. These cases are thought to be the first significant patent infringement actions relating to mRNA vaccines and it is therefore going to be interesting to see how they play out. Interestingly, three of the five cases reported this year relate to patents covering the LNPs, which may point to a broader trend in future litigation (and the types of patent it may actually be possible to obtain).

In each of these cases, the claimants are seeking damages for alleged patent infringement. However, interestingly, none of the claimants are seeking an injunction to prevent sales of the allegedly infringing COVID-19 vaccines. The lack of an injunction request is relatively unusual in patent infringement cases, but understandable given the circumstances of the pandemic; attempting to prevent the supply of the vaccines could result in a PR disaster and may also be refused by the relevant courts in any event. For example, injunctions are a discretionary remedy in the UK and there are also legal provisions such as compulsory licenses and Crown Use provisions that could potentially be relied upon to avoid patent infringement in times of emergency.

### Arbutus & Genevant vs Moderna

In February 2022, Arbutus and Genevant filed a patent infringement case against Moderna in the US District Court of Delaware. Arbutus and Genevant are alleging that the production and sale of Moderna's COVID-19 vaccine infringes six US patents [16] relating to LNPs and their use. According to the claim, the relevant patents are owned by Arbutus and licensed to Genevant and relate to structural lipids, such as phospholipids and cholesterol; cationic lipids, including ionizable lipids that are positive charge-bearing at certain pH levels; and conjugated lipids, which are lipids attached to a polymer such as polyethyleneglycol (PEG).

Moderna denies infringement of the relevant patents. As an interesting aside, Moderna is also claiming that Arbutus and Genevant have brought the claim against the wrong party in the wrong court. Moderna's position is that it is a US Government-contracted supplier as part of the US' emergency pandemic response and is therefore protected from patent infringement actions under US Code Section 1498 which would require the claim to be brought against the US Government in the US Court of Federal Claims [17].

### Acuitas vs Arbutus & Genevant

As mentioned above, Acuitas partnered with BioNTech and Pfizer to license the LNP used in the Pfizer/BioNTech COVID-19 vaccine (Comirnaty). In March 2022, Acuitas brought a claim against Arbutus and Genevant in the US District Court for the Southern District of New York seeking a declaratory judgment


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that the Pfizer/BioNTech COVID-19 vaccine does not infringe nine patents owned by Arbutus [18] and that the relevant patents are invalid in any event. The nine patents in question include the six US patents under which Arbutus and Genevant are suing Moderna (referred to above).

## Alnylam vs Pfizer & BioNTech

In March 2022, Alnylam filed separate patent infringement cases against Moderna and Pfizer in the US District Court of Delaware. Alnylam alleges that the Moderna and Pfizer/BioNTech COVID-19 vaccines infringe one of its US patents which claims a class of cationic biodegradable lipids that can be used in the formation of LNPs for the delivery of an active agent, including mRNA. Both Moderna and Pfizer deny infringement. Moderna again is also seeking to rely on US Code Section 1498 claiming that the suit should have been brought against the US Government in the US Court of Federal Claims.

In June 2022, Alnylam filed new patent infringement suits against Moderna and against both Pfizer and BioNTech, each in the US District Court of Delaware. These latest cases allege that the companies' respective COVID-19 vaccines infringe a recently granted US patent, which also claims a class of LNPs that can be used in the formation of LNPs for the delivery of an active agent, including mRNA.

## CureVac vs BioNTech

In June 2022, CureVac filed a lawsuit in the German Regional Court in Düsseldorf against BioNTech SE and two of its subsidiaries, alleging that the Pfizer/BioNTech COVID-19 vaccine infringes four of CureVac's German patents relating to the engineering of mRNA molecules [19]. The related press release by CureVac states that the patents relate to sequence modifications to increase stability and enhance protein expression, as well as mRNA vaccine formulations specific to COVID-19 vaccines. At the time of writing, BioNTech has responded, without naming CureVac, via a statement posted on its website that"BioNTech's work is original, and we will vigorously defend it against all allegations of patent infringement".

## BioNTech & Pfizer vs CureVac

Following the German action brought by CureVac against BioNTech (referred to above), BioNTech has responded, together with Pfizer, by bringing a claim against CureVac in the US District Court for Massachusetts seeking a declaratory judgment that the Pfizer/BioNTech COVID-19 vaccine does not infringe three US patents owned by CureVac relating to mRNA vaccines [20].

## OUTLOOK FOR THE FUTURE

The synthetic mRNA field is still relatively young, but innovation is continuing at a rapid pace. The COVID-19 vaccines have demonstrated both the extraordinary utility of the technology and the potentially phenomenal value of mRNA products. With companies investing significant sums into their mRNA development efforts and a growing number of partnerships in the field fueling development, the patent landscape relevant to mRNA vaccines is likely to become even more crowded and complex. As such, it seems likely that there will be more patent challenges and potential infringement actions in the near future as companies jostle for position in the market. For anyone involved in the field of mRNA vaccine development, the complexity of the patent landscape and the recent litigation in the field should act as a reminder of the importance of involving patent specialists early in development in order to navigate freedom to operate issues, patent filing strategies and patent licensing negotiations.

With almost inevitable freedom to operate issues and a specter of potential litigation, an

increasingly complex and fragmented patent landscape may also catalyze the formation of new collaborations and cross-licensing partnerships. Particularly between mRNA vaccine developers and companies specializing in delivery technology such as LNPs. A focus on solving freedom-to-operate issues may also lead to a degree of consolidation in the market and potentially an uptick in M&A in coming years as companies look to secure access to patents underpinning key elements of their mRNA platforms.

Finally, much has been said during the pandemic about the role that patents play in innovation and whether they enable or hinder development and access to new technologies. The pandemic has also given rise to a broader debate on issues of public interest such as access to medicines (particularly in lower-income countries), drug pricing, public funding, commercial profit, and the link between each of these issues and the patent system. While those broader issues are outside the scope of this article, the recent proliferation of patent infringement actions relating to the use of LNPs in mRNA vaccines is interesting in this context. We will have to wait to hear the outcome of those cases, but it already seems clear that the development of Moderna and Pfizer/BioNTech's COVID-19 vaccines were not impeded by patents. Even if the vaccines are shown to infringe, the claimants are not seeking injunctions to prevent sales. Ultimately then, the patent litigation in this instance should have no direct impact on the public's access to the COVID-19 vaccines. However, a large and complex patent landscape can become an issue if companies find themselves burdened with so many third-party royalty obligations that commercial incentives to bring a product to market are reduced. Similarly, if patent protection on the mRNA vaccine and its use is difficult to obtain, this could also discourage companies from developing such products for fear of not being able to recoup their investment costs during the period of any patent term. While there is no suggestion that any mRNA vaccine developers are currently in this situation, it will be interesting to see how all of these issues develop in the years ahead.

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17. The effect of US Code Section 1498 is to provide that if the United States, or contractors acting on its behalf, infringes a US patent, the patent owner's remedy is an action for compensation against the United States in the United States Court of Federal Claims. It therefore generally protects US government contractors from liability for infringement.

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INTERVIEW

# RNA vaccine production 4.0

**Charlotte Barker**, Editor, *BioInsights*, speaks to **Zoltan Kis**, *Lecturer, Department of Chemical & Biological Engineering, University of Sheffield.*

**ZOLTAN KIS** is a Lecturer at the Department of Chemical and Biological Engineering, University of Sheffield. Previously, he was a Research Associate in the Future Vaccine Manufacturing Research Hub at the Sargent Centre for Process Systems Engineering, Department of Chemical Engineering, Imperial College London, modeling COVID-19 mRNA vaccine production. He gained his PhD in Bioengineering from Imperial College London in 2015. When the COVID-19 pandemic hit, Zoltan Kis was part of a group working on computer modeling of RNA vaccine production. As it became clear that mRNA vaccines would be crucial to the pandemic response, the team was called on to advise global organizations on how best to produce the vaccines at scale. Now, he is leading a new project at the University of Sheffield, developing platform processes for faster, more efficient production of RNA vaccines. We spoke with Kis to find out more.

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**Q** What led you to specialize in modeling vaccine manufacture?

**ZK:** I have a background in chemical engineering, biotechnology, and bioengineering. I was always interested in practical applications of basic science – how to scale up and disseminate innovative products in the real world so they have an impact on people's lives. So, when an opportunity arose in 2018 to join the Future Vaccine Manufacturing Research Hub

at Imperial College and use modeling to determine how best to manufacture mRNA vaccines, it was a great fit for me!

**Q** Can you give an overview of your work at the Future Vaccine Manufacturing Research Hub?

**ZK:** I was part of a large collaborative project, involving both academic and industry partners. My work focused on two types of computer modeling: techno-economic and quality by design.

Techno-economic modeling aims to optimize the entire production process to reduce costs and increase productivity.

Quality by design modeling looks at how we can link product quality with the production process, with the goal of replacing conventional quality testing with a more flexible, real-time testing approach. Instead of testing after every production batch, we would do extensive real-time testing to analyze the product and if those tests show that the product is meeting specifications, the product can be released in real-time. This could work hand-in-hand with real-time release and real-time monitoring of vaccines, and it would also help a lot in developing continuous production processes.

**Q** You started that work before the COVID-19 pandemic hit. How did things change when mRNA vaccines became the frontrunners in the global race for a vaccine?

**ZK:** It was a dramatic change! Our work focused on modeling RNA production processes and determining how to scale up and manufacture vaccines for large numbers of people. That was unusual because, at the time, people were mostly viewing RNA as a personalized cancer therapy.

That put us in quite a unique position, and we were contacted by people from many different organizations – academics, non-governmental organizations, media, and companies – all of whom wanted to know how RNA production could be implemented at a very large scale. At times, the interest was almost overwhelming, but we talked to as many people as we could and helped as much as we could.

**Q** And what is your current focus?

**ZK:** Last September, I joined the University of Sheffield, and I'm now leading a large project aiming to innovate RNA production processes. The plan is to

> "Our end product is not a single vaccine – it is the manufacturing technology, which will then enable us to make vaccines and therapeutics against many different diseases, very quickly."


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develop a platform technology that we can use to produce different vaccines and therapeutics based on RNA for different diseases. These production processes should also produce different RNA formats, including conventional messenger RNA, self-amplified RNA, and circular RNA. We have several very ambitious objectives:

- High productivity of 50 g of RNA per day, achieved by scaling out the process.
- Low-cost production. For example, making antibodies based on RNA at a cost of below $US10 per dose.
- High quality, with around 25 critical quality attributes to optimize.
- Processes that are easier to operate, robust, and suitable for distributed manufacturing, allowing a network of distributed manufacturing facilities around the world to produce vaccines rapidly for an outbreak.
- Rapid development and mass production of products.

## Q How will you achieve this?

**ZK:** There are several key enablers. One is that we are developing these production processes as a platform and using the quality by design framework to closely link the product with the process through the critical process parameters.

There are some real challenges in monitoring product quality in real-time. To address that, we are developing what we call 'soft sensors' – computer models that indirectly quantify critical quality attributes.

We are also developing digital twin models for the production process, which simulate the process in real-time and use it to predict product quality in the next 5–10 min, allowing corrective measures to be initiated. This is known as model predictive control. Together, these digital approaches, using soft sensors and digital twins, will enable continuous production.

In a batch process, conditions vary – as the batch progresses from the beginning to the end of the batch, reagent concentrations and reaction rates will change. By contrast, in a continuous process, you can achieve a steady state, maintaining optimum values throughout the process to maximize efficiency.

## Q What's the ultimate goal of your work?

**ZK:** Our end product is not a single vaccine – it is the manufacturing technology, which will then enable us to make vaccines and therapeutics against many different diseases, very quickly. The antigen or target protein might change, and that will require some validation in a clinical setting, but the underlying production technology and quality control would stay the same.

The technologies we are developing, which include both physical devices and computational tools, will enable a rapid response to future epidemic or pandemic threats. We hope this will also accelerate the regulatory approval process because we can transfer our platform knowledge from one product to the next.

**Q** What do you see as the key advantages and challenges of mRNA vaccines?

**ZK:** Most importantly, mRNA technology is much faster – both in developing a new candidate vaccine and in mass producing that vaccine once the infrastructure is in place. mRNA or self-amplifying mRNA vaccines for COVID-19 can be up to 10,000-times faster to produce compared to the viral vector vaccine.

This is a platform technology, which means that you can make multiple products with the same infrastructure – the same production flow, quality control approaches, and experts. Everything stays the same except the template DNA. That allows us to set up the infrastructure for rapid response production before an outbreak occurs, so we can rapidly produce candidate vaccines for clinical trials, and the resulting approved vaccine.

Many of the challenges come from the fact that it's a very new technology so there is limited know-how in the industry. Some of that know-how is also protected by patents, such as lipids used for formulation, or specialized capping reagents.

Another issue is stability. Currently, these vaccines have to be stored at very low temperatures to prevent degradation. That is not ideal, especially in countries where there is limited capacity for ultra-low temperature cold chains.

**Q** Where do you hope to see the field heading?

**ZK:** I believe that, as time goes by, we will see lots of development in this field. It's still a very new product category, and it has already been shown to be effective and safe.

There's a lot of research into more thermostable formulations to remove the need for cold chain distribution, and I'm hopeful we'll see those bear fruit in the next 5–10 years. Then there are new products being developed, such as self-amplifying or circular RNA platforms, which could be applied to vaccines or protein-replacement therapy.

We will see more human vaccines approved and, as production costs fall, we might even see veterinary vaccines based on RNA, which typically require a much lower cost per dose.

One obvious target for an mRNA vaccine could be influenza because flu vaccines have to be updated annually. Currently, the vaccine composition is chosen more than 6 months ahead of flu season, meaning that

> "RNA technology would allow faster development cycles for a vaccine so that we could produce a flu vaccine that is more likely to protect against that year's strains."


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the vaccine is not always a good match for the predominant strains. RNA technology would allow faster development cycles for a vaccine so that we could produce a flu vaccine that is more likely to protect against that year's strains.

I hope to see the development and application of a full quality-by-design framework to the mRNA platform. It will take significant effort but there are big advantages. Both the RNA platform and quality by design framework are disease-agnostic. Once they are co-developed and integrated, we will have a powerful platform to develop and mass produce rapid-response vaccines to protect us from future pandemic threats.


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FASTFACTS

# End-to-end solutions for mRNA development and manufacturing

**Susana Domingues-Vallon**, Global Subject Matter Expert, mRNA Pharma Services, Thermo Fisher Scientific

**The mRNA therapeutics field has experienced an incredible increase in both challenges and opportunities, and developers are racing to the clinic at an unprecedented pace. Combining a flexible approach to development and manufacturing with critical foundational capabilities like comprehensive mRNA analytics and extensive experience with sterile injectables enables the speed required to succeed in today's rapidly evolving mRNA market. This poster provides an overview of Thermo Fisher Scientific's flexible mRNA development and manufacturing services that are backed by decades of therapeutic manufacturing expertise to get you to market faster.**

Thermo Fisher Scientific has built upon over 30 years of sterile injectables and advanced therapy GMP manufacturing experience to now provide mRNA development and manufacturing services out of their Monza, Italy campus **(Figure 1)**. Services include GMP plasmid, mRNA, and lipid nanoparticles (LNPs) process development, cGMP manufacturing, and analytical development and testing. In addition, the services provide access to an integrated supply chain that leverages an extensive global network of raw materials, equipment, and temperature-controlled storage and shipping solutions.

## PROCESS DEVELOPMENT

The first step in manufacturing for any therapeutic product is robust process development. That's why Thermo Fisher Scientific's process development services follow a methodical, risk-based approach to clinical and commercial readiness that ultimately saves time and reduces cost **(Figure 2)**. For mRNA specifically, processes assessed include plasmid linearization, mRNA synthesis scale-up and optimization, lipid formulation and solvent removal development, analytical method development and qualification, as well as fill-finish services such as formulation and lyophilization process development and optimization.

## SUMMARY

mRNA therapeutic developers have the option to leverage the full suite of integrated services or just choose those that help fill immediate gaps in their capabilities or capacity. Start your mRNA project today with a flexible service offering backed by decades of therapeutic manufacturing expertise **(Figure 3)**.

**Figure 1.** Therapeutic mRNA development and manufacturing capabilities in Monza, Italy.

**Non-GMP development**
- 1,420 ft² process and analytical development laboratory
- Process characterization studies
- Lab batches (<1 g)
- Scale up studies

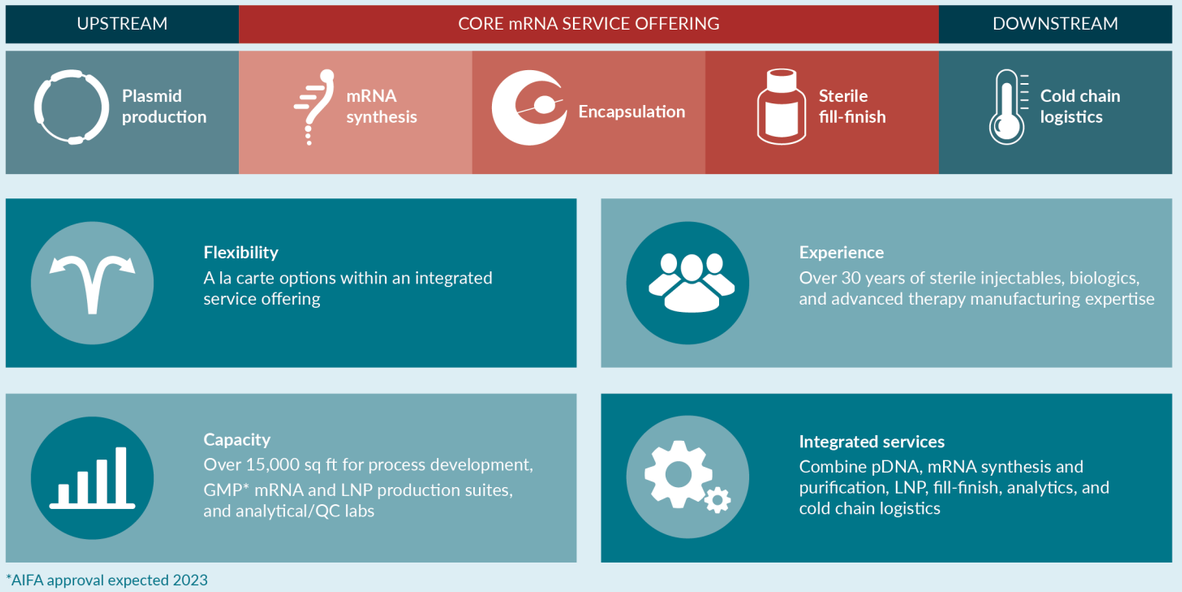
**cGMP manufacturing**
- AIFA approval expected in 2023
- 10,800 ft² dedicated cGMP platform
- 3 process trains, 1 g to 100 g mRNA/batch scale
- 2 lipid nanoparticle formulation areas
- In-house storage and buffer area
- Clinical to commercial

**QC and analytical**
- 1,500 ft² of QC labs
- Standard analytical, in-process testing and release
- cGMP method transfers, validations, and stability analytical capabilities in continuous expansion, with wide possibilites to adapt to customer needs

**End-to-end approach**
- Integrated supply chain for raw materials, single-use system, equipment
- Global network of expertise
- From starting material to fill finish (11 filling lines)
- Storage in temperature-controlled storage

**Figure 2.** A methodical, risk-based approach to process development.


**Figure 3.** Summary.




*AIFA approval expected 2023

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# VACCINE INSIGHTS

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COMMENTARY

# Healthcare in global crisis: preparations needed during the COVID-19 pandemic

**Bhavna Lall, Dhruva Chaudhry*, Shmuel Shoham, Onder Ergonul, Suneela Garg*, Peter Hotez, Maria Elena Bottazzi, Yanis Ben Amor, J Peter Figueroa, Sarah Gilbert, Mayda Gursel, Mazen Hassanain, Gagandeep Kang, David Kaslow, Jerome H Kim, Heidi J. Larson, Denise Naniche, Timothy Sheahan, Annelies Wilder-Smith, Samba O Sow, Prashant Yadav, Nathalie Strub-Wourgaft, Carolina Batista**
Lancet Commission on COVID-19 Vaccines and Therapeutics Task Force
*Lancet Commission on COVID-19 India Task Force

COVID-19 has led to more than 6 million deaths around the world [1]. Healthcare systems globally, with many already under crisis prior to the pandemic, have been impacted tremendously since the pandemic began. Leadership in each country and globally had to find ways to mitigate surges, while also having effective plans in place for timely responses with adequate access to interventions. As COVID-19 variants [2] surge with a persistent lack of sufficient vaccine coverage, the global healthcare community continues to require a comprehensive multidisciplinary approach to deal with the ongoing COVID-19 pandemic, where vaccination plays a vital role in mitigating the pandemic in addition to nonpharmaceutical interventions and therapeutics. Cooperation is urgently required between nations, community leaders, the scientific and healthcare community, global leaders, and industry to manage COVID-19 variant surges globally, as well as the spread of emerging pathogens, while focusing on prevention, testing, treatment, and healthcare and supply chain infrastructure and development.

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The COVID-19 pandemic is far from over and variants continue to evolve and spread globally. Scientists, healthcare professionals, public health officials, policymakers, and leaders face challenges making informed timely decisions and providing evidence-based guidance to guide their constituents and populations.

Since the beginning of the pandemic, non-pharmaceutical interventions (NPIs), also known as public health and social measures (PHSMs), such as hand washing, masks, physical distancing, and lockdowns played key roles in mitigation strategies [3]. We now have vaccines and therapeutics as additional powerful tools to control the pandemic. COVID-19 vaccines have succeeded in decreasing disease severity, viral spread, and mortality. However, inadequate (worldwide and regional) vaccine coverage due to lack of access, vaccine hesitancy [4], and other factors have contributed to COVID-19 surges in many parts of the world, compounded and exacerbated by the spread of new variants. These surges in turn led to severe shortages and in some cases the collapse of healthcare services in areas with low vaccination rates, especially during the delta variant surge. The experience in the southern United States in summer 2021 in states with low vaccination coverage demonstrates how the downstream effects of vaccine hesitancy can cripple local healthcare systems in even the wealthiest of countries [5]. And the experience in many low - and middle-income countries (LMICs) serves as a stark example of the catastrophic results of inadequate COVID-19 vaccine coverage, especially as new variants spread.

In April–May 2021, the delta variant-mediated COVID-19 wave surged in India, leading to mortality that was likely much higher than the officially reported 400,000 deaths [6]. Although the majority of vaccine doses contributed to COVAX were manufactured in India [7], vaccination coverage in this country of approximately 1.4 billion was under 5% at the time [8]. During the peak of infections, there were shortages and outages of oxygen, prompting a public outcry regarding need for critical oxygen supply for hospitalized patients as well as sick patients needing home oxygen due to inability in obtaining hospital beds. There were also shortages of critical medications and hospital beds. Clinical staff were stretched beyond safe limits. Widespread use of ineffective therapies such as ivermectin, doxycycline, azithromycin, and mixtures of Ayurvedic medicines may have exacerbated the crisis. Updated guidelines were provided at both the national and state levels but were frequently modified and often at variance with each other. Social media became the driver for prescribing practices, which were often not evidence based. Glucocorticoids were frequently misused. In desperation, people purchased novel therapies such as remdesivir and tocilizumab on the open market and at exorbitant prices, but without assurances of origin and quality. By the time the supply chains of oxygen and medications were streamlined and restored, significant damage had been done. India then faced another crisis. An unprecedented wave of COVID-19-associated mucormycosis cases (over 47,000 from May–July 2021) ensued [9], possibly due to overuse of steroids (including dexamethasone or equivalent) and the high diabetes/pre-diabetes prevalence in India, potentially causing an increased number of mucormycosis cases with a case fatality rate of approximately 36.5% [9]. The acute incidence of this epidemic of life-threatening fungal disease created critical shortages and price surges of key antifungals such as amphotericin B and Posaconazole [10].

The disruption of healthcare services due to COVID-19 affected all countries worldwide, with disproportionate impact on LMICs due to chronic suboptimal investments in health infrastructure and less resilience to recover. New surges of COVID-19 and emerging pathogens could cripple countries in the future. In times of medical crisis secondary to COVID-19, irrespective of variants, the healthcare and political leadership in each country and globally must find ways to mitigate surges while also having effective plans in place for timely responses with adequate access to interventions and healthcare.


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Countries need to have robust surveillance in place, or they will continue to be unpleasantly surprised at the spread of new variants. Once COVID-19 cases begin to increase, it is critical to take early measures to control disease spread and transmission. Delayed action results in increased cases and mortality as well as severe stress on healthcare systems for all patients and healthcare workers and staff. With oral therapeutics now available in some countries, COVID-19 is being managed effectively in the outpatient setting even for high-risk populations for those who have access to these drugs. Widespread availability and access to these drugs are urgently needed worldwide. However, current oral therapeutics still require patients to present early after symptom onset (within five days of symptoms) and cannot be administered to all due to the potential of drug–drug interactions with some therapeutics. In order to promote early access, best practices and availability of diagnostics, prevention, and therapeutics must be in place and immediately implemented. A linear response to an exponentially increasing threat will result in failure and lead to crisis. We propose the following three-pronged approach:

## PREVENTION

National pandemic preparedness plans should be developed and revised based on lessons learned from prior surges. The World Health Organization (WHO) should continue to assist countries in identifying gaps, establishing best practices, and setting targets for implementation.

Countries should establish, with support as needed from international donors, a sentinel surveillance system that includes routine monitoring and sequencing for variants. This needs to be coupled with tailored and effective community engagement.

COVID-19 vaccines must be universally available, accessible, affordable, and meet necessary safety, quality, and regulatory standards. This will require sustained financial commitments and increased manufacturing of vaccine products. But, without investment in capacity and infrastructure for countries to manufacture and deliver vaccines, and sustained efforts to gain public trust, vaccine doses will go to waste [11,12]. The latter will require consistent messaging and active engagement of susceptible populations and communities. Incentives should be designed to ensure ease of access to vaccines including transportation to vaccination sites, compensation for time off work to allow for vaccination and days off if needed post-vaccination, and additional methods to mitigate the indirect and out-of-pocket cost of accessing the vaccines.

Vaccines must be affordable, easy to store, and accessible. Policies should be feasible to implement and ensure equity and prioritization of vaccines based on scientific and medical data.

Health systems should be supported or augmented to be able to implement vaccine policies in a timely manner.

Misinformation should be addressed with strong community engagement and co-design of locally appropriate, fact-based messages. Scientific literacy for all policy and country leaders is necessary to guide public messaging. Vaccine hesitancy, willingness to be diagnosed, physical distancing, and mask-wearing are all areas where misinformation has resulted in setbacks in promoting accurate spread of information.

Research into improved vaccine thermostability and innovative methods for real-time extension of shelf-life information on vaccine batches should be encouraged to reduce vaccine wastage and simplified delivery. Vaccines should also be adjusted to new variants as needed.

Vaccination of vulnerable, marginalized, and high-risk populations, including health care and front-line workers, should be a priority.

In countries with large populations, policies such as allocation of vaccines to the private sector need to be mindful of both national and global guidelines to ensure

equitable and efficient distribution to their populations.

Boosters should be considered as per national policy and especially in moderately to severely immunocompromised people and high-risk populations.

With only 22% of the population of low-income countries vaccinated with at least one COVID-19 vaccine dose, wealthier countries must assist in vaccine equity and coverage worldwide [1]. Without vaccine equity and coverage on a global scale, variants will continue to develop and spread, and our current vaccines are at risk of becoming ineffective.

Investments should be made to boost sustainable manufacturing hubs in many low - and middle-income countries (LMICs)c for COVID-19 diagnostics, therapeutics and vaccines via technology transfer and capacity strengthening in chemistry, manufacturing and control (CMC) capacity, and other critical infrastructure needed to produce and administer quality interventions [13].

Community participation and political leaders need to emphasize proper mask wearing and COVID-19 protective behavior during surges such as avoiding large gatherings, indoor masking, and physical distancing to achieve control of the pandemic surges. In addition, contact tracing (when possible) and quarantine measures need to be enforced.

Universal availability of adequate PPE including N-95 face masks for health workers and at-risk front-line workers should be prioritized, as well as high risk populations/communities and all front-line workers.

Areas with known low vaccination rates should be targeted for preparatory measures to combat surges, as delineated in the next two sections.

Science and evidence should prevail and dominate the discourse, with attention to making key scientific findings and evidence accessible and understandable to lay audiences. Strong community and leadership support is required to counter COVID-19 misinformation on social media, in open or public forums, and from influential leaders (politicians, religious leaders, local and community leaders), public protests, information handouts, and other areas where misinformation is also being propagated.

## DIAGNOSIS & TREATMENT

- Accessing validated rapid diagnostic tests (RDTs), and polymerase chain reaction (PCR) is the first condition for access to treatment. Technical and resourcing support should be provided to ensure wide availability of antigen rapid diagnostic testing including community-based testing and self-testing to capture infections at the earliest stage of detectability so that the most suitable treatment options can be administered.

- Clinical guidelines should be consistent, evidence-based, widely accessible, and flexible to address local needs of communities. Guidelines should address all patients including hospitalized and outpatients as well as patient contacts.

- Adequate stocks of essential lifesaving drugs during the pandemic which now include oral antivirals nirmatrelvir/ritonavir and IV antivirals such as remdesivir as well as glucocorticoids such as dexamethasone, immunomodulators such as tocilizumab and baricitinib, currently effective monoclonal antibody cocktails, additional medications such as anticoagulants, antifungals, and antibiotics when needed, and critical oxygen supply must be maintained at levels sufficient to meet surge needs. Antibiotic stewardship should also be maintained during a surge. Key principles of how stocks and supplies can be transferred within a country between highly affected and non-affected regions/states should be investigated and negotiated before any surge. Oral therapeutics, IV remdiesivir, and monoclonal antibodies are being used to prevent severe disease and hospitalizations. Methods for rapid and affordable deployment of oral therapeutics and


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currently effective monoclonal antibodies, including in low-resource settings, should urgently be designed for those at primary need, i.e., at-risk populations. Efficacious oral treatments for outpatients need an immediate scalable production plan.

- The supply chain for oxygen (including production, transportation, storage, and distribution) must be prioritized, ensured, and supervised when oxygen supplies are noted to be in shortage. The oxygen shortage that was witnessed in multiple countries during the early part of the pandemic must never be repeated. Critically ill patients struggled to find oxygen for use in hospitals or at home during surges in multiple countries. The allocation of available oxygen supplies need to be managed through planning and monitoring [14].

- Medication and diagnostic prices in private markets where patients pay out of pocket must be controlled to ensure equitable and affordable access. Home care and triage protocols must be strengthened to ensure timely identification and safe transfer of patients to higher level care when needed.

- Research into oral treatments is still needed given the limitations of existing options. In addition, treatments may need to be adapted due to variant selection (e.g., monoclonal antibodies), to treat immunosuppressed patients, to prevent resistance development, and, ideally, to prevent or treat post-COVID conditions. Adequate funding to cover those critical research gaps is needed.

## HEALTHCARE INFRASTRUCTURE

Hospital beds, staffing, respiratory equipment, ventilators and supplies that will be needed should be prepared in advance of a COVID-19 surge. Infection Prevention and Control (IPC) teams in health systems should be adequately resourced to manage IPC supplies [15]. Temporary hospitals for treating mild-to-moderate cases of COVID-19 are also needed when home quarantine is not possible [16].

Adequate staffing of healthcare personnel such as physicians and nurses should be ensured prior to surges. During staff shortages, task shifting plans should be in place to train other healthcare workers, including medical and nursing students and resident trainees, in COVID-19 care. Mental health needs for healthcare worker teams must also be addressed during this time.

Command and control communication systems should be prepared ahead of time to ensure coordination, facilitation, and safe transportation of sick patients from rural areas and homes to hospitals.

Healthcare systems must be strengthened, especially at the primary care level to ensure equitable access to diagnostics, therapies, and vaccines. Healthcare and public health systems should be responsive and able to test, track and treat in a timely manner and have access to tools such as rapid antigen testing (AgRDT).

Capacity for advanced virology (e.g., genomic sequencing) should be considered a necessity and at least 5% of detected samples should be sequenced. The system for pathogen genomic sequencing in LMICs is nascent and will require technical and financial support to achieve these targets.

There is an urgent need to vaccinate equitably to prevent the spread of this pandemic and to ensure therapeutics are readily available worldwide. We need a comprehensive multidisciplinary approach to deal with the ongoing COVID-19 pandemic, where vaccination will play a vital role in mitigating the pandemic in addition to non-pharmaceutical interventions and therapeutics. We must scale up vaccine and therapeutics production, encourage unhindered supply, and ensure that infrastructure for delivery is in place globally. This will require coordination between governments, vaccine producers,

pharmaceutical companies, and community leaders to save lives and ensure equity. In turn, this will prevent the spread of more coronavirus variants and accelerate the decline of the pandemic. In addition, vaccine developers have a moral duty to support vaccination campaigns in LMICs to establish and expand infrastructure and vaccine manufacturing capacities. It is also essential for the current and future global pandemics that intellectual property rights for vaccines and therapeutics that are deemed essential worldwide do not prevent widespread deployment. As part of global efforts for pandemic preparedness, global health leaders and multilateral organizations should leverage on intellectual flexibility frameworks to ensure equal access for vaccines and therapeutics that are deemed essential.

Simultaneously, as the world's population is yet to be fully vaccinated, we must be prepared to manage cases of COVID-19 with adequate infrastructure, diagnostics and therapeutics. Cooperation and solidarity are urgently required between nations, community leaders, the scientific and healthcare community, global leaders, and industry. The time is now for such a collaboration to address the needs of the healthcare communities worldwide that are being impacted by the ongoing crisis and support the infrastructure that is so desperately needed.

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INTERVIEW

# Access to vaccines: how can we leverage technology innovations to achieve greater vaccine equity?

**Charlotte Barker**, Editor, *Vaccine Insights*, speaks to **Fatema Kazi**, R&D Blueprint and Covid 19 Vaccine Development, WHO

**FATEMA KAZI** is an Immunologist working at the WHO's R&D Blueprint Team–part of the Health Emergencies and Preparedness Response. Previously, she has worked at the Elizabeth Glaser Pediatric AIDS Foundation, GAVI, UNOPS, The Stop TB Partnership, and the Global TB Programme (WHO) focusing on research and development in innovative therapeutics, vaccines, and diagnostics. She has a PhD in Cellular Immunology and Infectious Diseases from the London School of Hygiene and Tropical Medicine, and pursued her postdoctoral career as a Senior Immunologist Research Fellow at Leiden University Medical Centre and the University of Oxford, as well as training as a molecular biologist for the Ministry of Defense, UK. In response to the pandemic, Fatema has been leading projects at WHO related to tracking, monitoring, and assessing the development of the COVID-19 vaccine candidates worldwide, conducting epidemiological reviews of vaccine effectiveness against variants of concern. She is now evaluating vaccines for Monkeypox, Lassa Fever and Sudan ebolavirus in response to the current outbreaks.

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Fatema Kazi works for the WHO, where she helps to assess the public health value of vaccine products and technologies in routine, campaign, and outbreak settings. We caught up with her to discuss how innovations in vaccine technology can help get vaccines to the people who need them.

## Q How did you get involved in the vaccines field?

**FK:** My journey into this field started when I was a child in the 1970s, living in Nigeria. My father took me to a busy clinic to get my childhood vaccinations, and I remember being completely bowled over (and terrified!). My father said: "Do you know that the medicine you're getting saves people's lives and helps them live much longer?"

I understood at that moment that this was something really important, so as I got older, I started asking a lot of questions to understand why we take these jabs. I then became interested in biology and immunology and continued to be fascinated by vaccinations.

Later we moved to California, and I remember being at a flea market at the age of 12. I came across a microscope, and as I looked down the eyepiece, and I could see bacteria, tissue, and cells I became very excited and I clearly remember asking the seller what it was, and he handed me a book on bacteria. The first page was about Alexander Fleming identifying penicillin, and I was amazed! At that very moment I decided I would be a scientist.

I studied microbiology at university and eventually specialized in immunology. I wanted to understand how our immune systems work to fight infections because I believe that is the key to understanding how to design and develop vaccines. Eventually, I was lucky enough to work in academia as a researcher in immunology, and eventually to run a research project looking at how to design vaccines against TB.

Ultimately, I wanted to be able to apply all of this knowledge in a context that would make a difference, so I decided to move into global health. Now, I work in the field of COVID-19 vaccines, pulling together all my experience as an immunologist and in the lab and applying it to this pressing global health challenge.

## Q What is your role at WHO?

**FK:** I work in a team known as the research and development (R&D) Blueprint, situated within the Emergencies Unit of WHO.

The role of the R&D Blueprint is to work across the globe with experts in research and development to help develop diagnostics, therapies, vaccines, and strategies for emergency pathogens, such as Ebola, Zika, and Nipah virus. With the pandemic, COVID-19 became part of this list.

I focus on the vaccine component of our work, in particular on COVID-19. Since the pandemic, I've been working with developers, academics, and various global organizations to monitor and track all the COVID-19 vaccines that are being developed worldwide, from concept right through to clinical trials and approval. Right now, there are 359 COVID-19 vaccines in preclinical and clinical development–161 in the clinical pipeline, and almost 200 in the preclinical phase, with more being developed. We use this data to analyze and inform scientific and evidence-based decisions made at the research and policy level, by various types of stakeholders.

I work closely with academic institutes and other evidence-based organizations to assess the data on the effectiveness of COVID-19 vaccines, examining and re-analyzing the existing data to


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assess the strengths and the weaknesses of the different vaccines, so that we can give a transparent and pragmatic view on the data being generated. This type of analysis has been critical during the pandemic. There are so many voices, platforms, and perspectives, from individuals, to specialized organizations, and governments that end up giving their interpretations of the data. Therefore, we aim to present the data transparently and without any bias.

"For both existing and new vaccines, we're constantly looking for innovations to address challenges and barriers; in particular, for people in low and middle-income countries (LMICs)."

The R&D Blueprint team gathers information from across the global research community to create roadmaps, so that we can understand what research we need to do, what are the gaps, strengths, and weaknesses, and how can we support different research teams around the world to ensure that the best data is generated.

**Q** How can technology innovations improve vaccine delivery and ultimately vaccine equity?

**FK:** For both existing and new vaccines, we're constantly looking for innovations to address challenges and barriers; in particular, for people in low and middle-income countries (LMICs).

With COVID-19, a number of vaccines became available very quickly, but LMICs have been unable to access them due to challenging logistics and high costs. mRNA vaccines require ultra-low temperature storage, and LMICs have found it difficult to accommodate the kind of infrastructure needed.

We look to technology innovations to help us solve these problems. Looking at issues with the cold chain, there is a lot of research into improving formulations to withstand temperature changes so the vaccines are more heat stable.

There are also monitoring labels, which stick to the vaccine vials and monitor temperature changes to identify any vials that have been outside of their storage temperature range for too long and should no longer be used. These technologies are already being used and are now being adapted to different vaccines and scenarios.

Even the type of container you put the vaccine product in can make a real difference in addressing some of the challenges in vaccine delivery. For example, compact, prefilled, auto-disposable devices reduce the storage volume, are easier to administer, and prevent contamination

Finally, there are some interesting needle-free vaccine technologies, that can improve the impact of the vaccine in activating the immune system.

For example, there are oral and sub-lingual formations, which immediately target a different part of the immune system in the oral mucosa. Tablet formulations also have the advantages of being less frightening to many patients, easier transport, and–importantly–removing the need

for trained healthcare personnel to administer doses.

However, many vaccines are not suitable for oral delivery, so other needle-free systems are needed. An alternative delivery method is a micro-array patch (MAP). This is a fascinating all-in-one delivery technology that can potentially address multiple immunization barriers by improving thermostability and ease of use.

"If we have one vaccine that can target many pathogens, that also brings down the cost and makes it less challenging to implement these vaccines in LMICs."

**Q** What has been the most impactful technology that you've seen emerge during the COVID-19 pandemic?

**FK:** I'm going to have to go with the mRNA vaccines, and I imagine a lot of people feel the same!

I've been aware of this technology for a long time and have seen clinical trials of mRNA vaccines for other diseases, such as Ebola, but the pandemic pushed this vaccine platform to center stage and it has been pivotal in controlling the pandemic.

Now that we have proof that this is a feasible technology to use, it's going to be applied to many other vaccine targets. It's been like a scientific revolution, quite frankly. Seeing this technology come to the fore has been so exciting, especially as it's been a very long time waiting.

Having had the advantage of working on all the COVID vaccines, I think the other impactful area is not just one technology but changing our mindset when we think about vaccines. For example, a lot of experts are now saying that we should think about designing vaccines not just for a particular pathogen or variant, but for whole families of pathogens. For example, several groups are working on pan-sarbecovirus or pan-coronavirus vaccines. In this way, we are preparing for future outbreaks, not just of SARS-CoV-2, but SARS-CoV-1, MERS, or potentially any other pathogen within this family.

If we have one vaccine that can target many pathogens, that also brings down the cost and makes it less challenging to implement these vaccines in LMICs.

**Q** What new technologies are you most excited to see emerge over the next 5 years?

**FK:** The one that comes to mind is MAPs and there is a lot of work going on within my network to push this forward. It's exciting because it's an easy technology to use. It's a bit like attaching a plaster to your body, very easy to apply, so in terms of training healthcare workers, it's going to be easier and faster. We're always trying to look for ways to


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prevent contamination and improve acceptability, and I think a lot of people will be quite happy to have a MAP attached to them rather than being injected with a needle. in terms of storage, it's a very small, compact tool. It doesn't require the same kind of refrigeration or storage criteria that your typical vaccine does.

This could be a technology that we look at for future emergencies as it addresses many challenges to vaccine equity, including acceptability, hesitancy, cold chain issues, and logistics issues. I think it's going to be a game changer, it's just a matter of time.

**Q** Is the future of vaccines needle-free?

**FK:** Perhaps.

Interestingly, there are studies out there indicating that some communities actually prefer to have the needle, because they believe that's what a 'real' vaccine is, that they are most effective. We will need to do a lot of research to understand how this technology is going to be accepted by different societies and communities that are accustomed to needle delivery.

The prospect of needle-free delivery is very exciting, but there are going to be a lot of challenges, and a lot more research and investment are needed.

**Q** How long might it be before we start to see MAPs making it onto the market?

**FK:** I would say 5–10 years. It's still in the early phases of research and as it wasn't used during the pandemic, it may have missed the boat for being pushed quickly through the pipeline.

A lot of work is being done to develop this technology for measles and influenza. These are important, critical diseases for which we will always need routine vaccination so investing in these disease areas to improve access to vaccination will hopefully accelerate its process through the R&D pipeline; and we must not forget the importance of funding to support these innovations.

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## AUTHORSHIP & CONFLICT OF INTEREST

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