

Has COVID-19 changed the future of pharmaceutical regulation?

Harriet Edwards^{a,*}

^a*Albumedix Ltd., United Kingdom*

Abstract

COVID-19, or SARS-CoV-2, has undoubtedly changed the world as we know it, affecting daily life, health, and economics to an unprecedented degree. Due to the widespread and devastating impact of this previously unknown virus, there has been a massive effort from the pharmaceutical industry to rapidly develop a vaccine to protect the population. As a consequence of the increasingly evolving threat of COVID-19, developers and regulators have had to respond accordingly, learning about the virus while attempting to develop and regulate treatments concurrently. As if this task was not complex enough, developers and regulators have had to face this challenge while simultaneously tackling arguably the largest widescale media attention and pressure that has ever been felt by the industry, with mainstream media, politicians, and the general public all having a vested interest in the development of the vaccines and an opinion on how they should be developed, distributed, and monitored. It is therefore a true testament to developers and regulators alike that many vaccines have already been authorized for use (or are about to be) in so many countries and territories across the world, in record time. However, this success brings many questions as to why other medicines have not been regulated at such speed before and whether the SARS-CoV-2 vaccines have received ‘special treatment’, with many posing the question: ‘are these vaccines actually safe?’. One thing that is clear, at least to the industry, is that the incredible flexibility, pragmatism, and creativity of developers and regulators in their approach to authorizing the vaccines has, unequivocally, been a main contributor to the rapid availability of these novel vaccines. This article aims to examine whether COVID-19 (SARS-CoV-2) has changed the future of regulation through identifying and discussing the notable regulatory milestones achieved over the course of the COVID-19 pandemic (to date), and critically analyzing the regulation of those successful vaccine candidates that have been authorized at the time of writing, while posing the ultimate question; has COVID-19 revolutionized the future of regulation of medicine development and authorization or are we simply responding to an unprecedented global pandemic?

Keywords:

COVID-19, SARS-CoV-2, mRNA Vaccine, AAV Vaccine, Advanced Therapy Medicinal Products (ATMPs), regenerative medicine, regulation, MHRA Conditional Approval, emergency use authorization

1. Introduction

The explosion and continued innovation of available advanced therapies, regenerative medicines, and personalized therapeutics over recent years has led to the pharmaceutical industry experiencing arguably the biggest paradigm shift with regards to regulation since the concept of regulation was properly introduced over 60 years ago.

These novel therapies, developed as a consequence of gigantic leaps in scientific and technological capabilities, knowledge, and expertise, are pushing the boundaries of what has previously been possible and challenging the idea of what modern medicine really means. Where most existing medicines look to treat patients’ symptoms, many of the advanced therapies are specifically developed with the ultimate goal of completely

curing and eradicating previously untreatable diseases. In order to achieve this goal, advanced therapies (a widely used umbrella term to capture this novel group of emerging innovative treatments) need to be different from existing, well-established medicines; therefore, where traditional medicines are typically simpler, well-defined chemical molecules, advanced therapies are usually complex biological molecules and/or have been genetically modified or manipulated in some way. As such, regulations have needed to change quickly to accommodate a completely different set of rapidly evolving and challenging products.

Given the incredible change in regulations to accommodate advanced therapies, could it be that one virus, (albeit one responsible for the largest global pandemic since the Spanish Flu), namely COVID-19 or SARS-CoV-2, is single-handedly responsible for a potential revolution in the way we regulate vaccines and, even more broadly, medicines in general, to change the face of pharmaceutical regulatory affairs as we

*Corresponding author: Harriet Edwards,
Email: HAED@albumedix.com

know it today?

This article aims to explore whether COVID-19 (SARS-CoV-2) has changed the future of pharmaceutical regulation, through identifying and discussing the notable regulatory milestones achieved over the course of the COVID-19 pandemic (to date) and critically analyzing the regulation of those successful vaccine candidates that have been authorized for use at the time of writing. The extent of authorization, including the differences in regulatory documentation and the response by both the developers and regulators, will also be analyzed. The author will explore the potential future changes to regulation as a direct result of regulating SARS-CoV-2 vaccines, while posing the ultimate question; has COVID-19 revolutionized the future of pharmaceutical regulation or is this simply a response to an unprecedented global pandemic?

2. The Unique Challenges of SARS-COV-2 Vaccine Development

While regulators responsible for reviewing the SARS-CoV-2 vaccines are facing the same challenges that they are also experiencing for the regulation of other Advanced Therapy Medicinal Products (ATMPs), particularly learning how to regulate this novel category of medicines in parallel to the developers discovering and manufacturing such products, these challenges are significantly amplified in the case of SARS-CoV-2. This may be due to some (not all) of the potential vaccines themselves falling into the regulatory category of ATMPs or regenerative medicines. However, more notably these greater challenges are as a consequence of the extreme global pressure that regulators are facing to ensure SARS-CoV-2 vaccines are available to patients in need as quickly as possible, while ensuring they are both safe and effective and therefore suitable for a mass rollout to an unprecedented scale. Regulators and developers (i.e., the pharmaceutical companies, scientists, and researchers responsible for creation of a SARS-CoV-2 vaccine) alike are facing unparalleled scrutiny and media spotlight, with mainstream media, politicians, and the public all having a vested interest in the development of the vaccines, and therefore, an opinion on how these products should be developed, distributed, and monitored.

With so many perceived unknowns about SARS-CoV-2, coupled with the rapid and devastating impact that the virus has had on many people's health and general daily lives, not to mention the global economy, developers have faced challenges in creating a vaccine that targets the most efficacious mechanism of action for a virus which, at the time of development starting, its genome was not sequenced. Granted, these challenges exist for developers targeting other previously unknown diseases or viruses, but for SARS-CoV-2 they have been further amplified to a level not experienced before due to the significant time pressure to develop a vaccine to deal with an increasingly devastating virus in real time.

The development of a SARS-CoV-2 vaccine was always going to be subject to increased scrutiny due to the far-reaching global impact of the virus; therefore, the time pressure placed

on developers has subsequently transferred to the regulators as the critical barrier between a potential treatment reaching the masses. This has forced developers and regulators to approach the successful development of SARS-CoV-2 vaccines with a level of pragmatism that has not been present before. It is therefore an unquestionable victory for the pharmaceutical industry in general (from developers, regulators, researchers, and beyond) that, at the time of writing this article, no less than four vaccines have been successfully authorized across the western world for the treatment of COVID-19, with more in review and even more in the development pipeline. In successfully developing, regulating, and distributing these vaccines, the pharmaceutical industry has overwhelmingly achieved something that many considered impossible at the start of 2020, and the possibilities shown when developers and regulators come together with a common interest should therefore be highlighted.

3. The Regulatory Journey for SARS-CoV-2 Vaccines - Utilizing Existing Measures for a Rapid Outcome

There is little doubt that the future of pharmaceutical regulation has the potential to change as a result of experiences during COVID-19. Although it is not yet known how extensive this potential change may be, it is fair to assume that this change will be particularly applicable and likely to be utilized again for responses to unforeseen pandemics and previously unknown diseases or viruses that affect a significant portion of the global population.

It is important to note that, regardless of territory, all of the vaccines currently authorized for use (or about to be authorized) have utilized some form of accelerated regulatory approval pathway in order to reach patients in need quicker than the standard regulatory review process allows. However, these pathways were not specifically designed for SARS-CoV-2 and have been utilized many times before for other medicines, including, but not limited to, vaccines, that comply with the appropriate regulatory requirements of each country or territory. Therefore, it could be argued that a potential regulatory approach is not in the route to approval, but in how that route has been exploited to its full extent.

Dependent on the country or territory in which the SARS-CoV-2 vaccines are submitted for regulatory review and authorization, there are slight differences in the pathways available and therefore differences in how the vaccines may be authorized for use. However, all regulators in key territories – defined solely for the purposes of this article as the United Kingdom, the European Union, and the United States – are working towards a common framework under the International Conference for Harmonization (ICH), and have mutual end goals to ensure vaccines are safe, manufactured to an appropriate quality, and are demonstrated to be efficacious, with a positive risk/benefit assessment for the intended patient. Therefore, the differences for approval are more semantic than fundamental, but still important to understand, since they will impact the logistical and operational delivery, in addition to availability, of each vaccine in the specified territory.

Table 1: Accelerated Pathways Used by SARS-CoV-2 Developers

Territory	Regulatory Authority	Accelerated Route	Definition	Important Features
Europe	European Medicines Agency (EMA)	Conditional Marketing Authorization (CMA)	The approval of medicine that addresses unmet medical needs of patients on the basis of less comprehensive data than normally required	<ul style="list-style-type: none"> • Rolling review of data • Dedicated reviewers assigned • Additional data submitted post authorization • Only valid for one year, renew annually and provide data required to transfer license to standard marketing authorization
United Kingdom	Medicines and Health Products Regulatory Agency (MHRA)	Conditional Approval (pre-Brexit) Regulation 174 (post-Brexit)	Medicinal product is authorized on a temporary basis in response to the suspected or confirmed spread of: (a) pathogenic agents; (b) toxins; (c) chemical agents; or (d) nuclear radiation, which may cause harm to human beings [1]	<ul style="list-style-type: none"> • Rolling review of data • Authorization is valid until expressly withdrawn by MHRA or upon issue of a full market authorization by the MHRA • Additional data and information may be requested at any time
United States of America	Food and Drug Administration (FDA)	Emergency Use Authorization (EUA)	The Commissioner may issue an EUA to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by a chemical, biological, radiological, or nuclear agent (CBRN) when there are no adequate, approved, and available alternatives [2]	<ul style="list-style-type: none"> • Data from interim analysis or incomplete trials may be used to issue the EUA • Conditions set forth by FDA including supply, chemistry, manufacturing, and control (CMC), safety data, and reporting

The accelerated pathways (i.e., routes to authorization or approval that are more streamlined or quicker than the standard approach to regulation) that have been utilized by SARS-CoV-2 developers in the key territories to date are briefly discussed in Table 1 to provide context to the reader; however, it is acknowledged that other accelerated approval routes are in existence in all of the territories discussed (but are not necessarily applicable for the SARS-CoV-2 vaccines, hence have not been included in this article).

4. Authorization or Approval?

The key difference between how SARS-CoV-2 vaccines have been approved between the U.S., UK, and the European Union is the use of temporary or emergency use authorizations (EUA) compared to the conditional marketing authorization (CMA) approval route [3]. Where the CMA takes all of the same rigorous steps and specific requirements with regards to legal rights, liabilities, monitoring, and safety as conventional

marketing authorizations, the EUA is not an authorization as such, and thus does not follow this approach. It is rather an authorization of the temporary use of an unauthorized medicine, albeit under specific conditions set forth by the regulator according to the emergency circumstances under which the use applies. Therefore, the EUA is more fluid and flexible to amend its requirements based on the emergency (in this case the COVID-19 pandemic), but it has different liabilities and legalities associated with the use of the medicine in question. The relative flexibility of an EUA allows the developer to submit partial or incomplete data, providing there is some evidence of a perceived benefit, but also allows the regulator to review and respond without predefined timelines to an application. Through an EUA, the regulator is not bound to the conditions of a typical marketing authorization, since the product in review is not being approved as such. Therefore, the regulator may set very specific conditions to the use of the unapproved medicine which may even be more stringent or specific than the usual conditions of approval. However,

it must be noted that, eventually, both the CMA and the EUA must be replaced by a full marketing approval (CMAs are renewed annually, EUAs do not have a set period for expiration) since these options are only temporary measures to deal with an unforeseen emergency and therefore do not give the SARS-CoV-2 vaccines ‘approval’, only authorization to be used during this unforeseen time.

Table 2 provides a comprehensive overview of the SARS-CoV-2 vaccines developed by and authorized (or likely to be authorised soon) in the key territories, identifying important differences in the vaccines and on the regulatory pathways and processes in how they have been authorized, along with the dates of first approval and the territories in which they are available. Similarly, Table 3 provides a less detailed account of additional vaccines, developed in other territories, acknowledging that the SARS-CoV-2 pandemic is global and therefore vaccines are being developed on a global scale.

5. Key Features of SARS-CoV-2 Vaccine Approval - Has COVID-19 Really Changed Future Pharmaceutical Regulation?

It is fair to comment that the speed at which the SARS-CoV-2 vaccines have been authorized is unprecedented. While accelerated regulatory pathways exist for the very purpose of enabling quick approvals to advance access of medicine to the market, the speed of the SARS-CoV-2 regulatory process is quite different to anything experienced before. The acknowledgment of rapidity has been further amplified by the fact that this is not isolated to one vaccine, or one country or territory; instead, there has been a combined global effort to provide rapid access to multiple vaccines over the last 12-15 months.

Not only has the speed of authorization been noteworthy, but coupled with the speed of developing the vaccines, from program initiation to a finalized product, it has unsurprisingly grabbed the attention of the public as well as the industry. However, where the industry can perhaps appreciate that no vaccine candidate has been given an ‘easy ride’ or skipped any of the rigorous safety and quality requirements mandatory for any vaccine (or other pharmaceutical product) in development, it is much harder for the public to fully understand this. This is particularly true when considering that the typical level of understanding of standard vaccine regulation is limited to the media headlines confirming that 6-8 years is the typical development timeline compared to 8-10 months for the SARS-CoV-2 vaccines.

It is undeniable that usually vaccines take much longer to be developed and complete the regulatory process than has been the case with the SARS-CoV-2 vaccines. However, it is entirely due to the combined efforts of the industry and the rapid response of the regulators, and of course, the developers of these vaccines, that they have been available to the public at such rapid speed.

Furthermore, it has only been possible for the regulators to authorize the use of SARS-CoV-2 vaccines so quickly due to a huge shift in prioritization of workload. Where regulators

would be simultaneously reviewing a number of applications, responses, and other information such as inspections, certifications, and audits, all of this work was deprioritized to allow a single focus on the COVID-19 pandemic. This has included the introduction of flexibilities or timeline extensions granted to manufacturers of other pharmaceuticals during the pandemic to allow the re-focussing of resources to deal mainly with the SARS-CoV-2 vaccines. Moreover, additional resources, whether these were existing resources working longer or being assigned solely to COVID-19-related regulatory activities or new resources, have allowed a rapid response to the vaccine applications submitted.

While all of these measures are highly commendable and provide a reasonable explanation for the rapid regulatory review of SARS-CoV-2 vaccines, it raises a critical question: is this feasible for future regulation of vaccines, or even further, of all medicines? Such intense and focused efforts may be possible for a relatively short and defined timeframe, but this surely cannot be considered an appropriate future way of working for the regulators. Based on this assumption, one could therefore argue that no such regulatory revolution is afoot.

Although the regulation of SARS-CoV-2 vaccines has undeniably changed the way in which regulators may approach the review of those deemed “important” applications, it cannot be sustainable on an overarching basis, and so this raises the question: what is the definition of “important” and what medicines could or should fall into this category? All developers would surely present a case for their product falling into this definition. This leads to an assumption that the changes in regulatory approach experienced during the COVID-19 pandemic can surely only be reserved for the exceptional circumstances we hope never to find ourselves in again.

6. Taking Advantage of Existing Regulatory Strategies to Maximize Flexibility and Speed to Market

Another factor that has played a role in the rapid regulation of SARS-CoV-2 vaccines is the pragmatism and flexibility of the regulators, particularly with their approach to out-of-the-box development programs. Arguably, this factor may be the stronger contributor to a future change in pharmaceutical regulation. Through the acceptance of flexible trial designs, combined clinical development phases, or the ability to review data based on interim analysis or in real-time, the stringent and strictly defined development programs that are currently the regulatory standard could be a thing of the past.

As is a common theme running throughout the regulation of SARS-CoV-2 vaccines, concepts and routes to regulation utilized by the developers are not new. However, the extent to which they have been employed or tested is more extreme than previously seen or accepted by the regulators; the use of a flexible or adaptive clinical study design is an example of this. Regulators have routinely accepted adaptive development programs for a number of years, although the flexibility or fluidity of the clinical program has been much less than seen in the SARS-CoV-2 clinical development programs. Typically for adaptive

Table 2: Current Approved Vaccines (as of May 2021)

Product Name	Company (Country)	Product Type	Mechanism of Action	Regulatory Package	Key Territories Approved In (Regulatory Route)	Date First Approved	Other Territories Approved In [4]
Comirnaty (tozinameran or BNT162b2)	Pfizer/ BioNTech (USA)	mRNA- mRNA sequence encodes for spike glycoprotein (S antigen)	Single-stranded 5'-capped mRNA encoding the viral spike (S) protein of SARS-CoV-2 in lipid nanoparticles delivered into host cells to allow expression of SARS-CoV-2 S antigen to elicit immune response [5, 6]	Non Clinical Trials: 4 pharmacology studies, 2 pharmacokinetic studies, 2 toxicology studies Clinical Trials: (participants) Phase I/II Trial (160), Phase I/II Trial (456), Phase II Trial (960), Phase II/III (43,998), Phase 3 (1,280)	United Kingdom (Temporary Use) USA (EMA) Europe (CMA)	02-Dec-2020 11-Dec-2020 21-Dec-2020	Argentina, Australia, Austria, Bahrain, Belgium, Bulgaria, Canada, Chile, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Iraq, Ireland, Israel, Jordan, Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Mexico, Mongolia, Netherlands, New Zealand, Norway, Oman, Philippines, Poland, Portugal, Qatar, Serbia, Romania, Saudi Arabia, Singapore, Slovakia, Spain, Sweden, Switzerland, UAE
Moderna COVID-19 Vaccine (mRNA- 1273)	Moderna (USA)	mRNA- mRNA sequence encodes for spike glycoprotein (S antigen)	mRNA delivered into host cells to allow expression of SARS-CoV-2 S antigen to elicit immune response to S antigen [7]	Non Clinical Trials: 7 pharmacology studies, 1 biodistribution study, 7 toxicology studies, 4 genotoxicity studies Clinical Trials: (participants) Phase I (120), Phase II (600), Phase II/III (3,000), Phase III (30,000)	USA (EMA) United Kingdom (Temporary Use) Europe (CMA)	18-Dec-2020 08-Jan-2021 06-Jan-2021	Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Mongolia, Netherlands, Norway, Poland, Portugal, Romania, Seychelles, Slovakia, Slovenia, Spain, Sweden, Switzerland
AZD1222 (Covishield)	Oxford University/ Astra Zeneca (United Kingdom)	Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S)	Monovalent vaccine composed of a single recombinant, replication- deficient chimpanzee adenovirus (ChAdOx1) vector that codes for the S glycoprotein of SARS-CoV-2	Non Clinical Trials: 6 pharmacology studies, 4 pharmacokinetic studies, 6 toxicology studies Clinical Trials: (participants) Phase I/II (256), Phase I/II (2,130), Phase I/II (1,112), Phase I/II (400), Phase II (100), Phase II/III (12,450), Phase II/III (1,600), Phase III (100), Phase III (40,000), Phase III (10,300)	United Kingdom (Temporary Use) Europe (CMA) USA	30-Dec-2020 29-Jan-2021 Not approved	Argentina, Austria, Belgium, Brazil, Bulgaria, Chile, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, El Salvador, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, India, Iraq, Ireland, Italy, Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Mexico, Mongolia, Morocco, Netherlands, Norway, Pakistan, Philippines, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, Thailand, Vietnam

Table 3: Other Vaccines Approved Developed by Non-Western Countries [8, 9]

Product Name	Company (Country)	Product Type	Mechanism of Action	Regulatory Pathway	Territories Approved in	Date First Approved
Sputnik V	Gamaleya (Russia)	Non-replicating viral vector	Adenoviral vector-based platform that codes for the S glycoprotein of SARS-CoV-2	Early Use Emergency Use	Russia, Algeria, Argentina, Belarus, Bolivia, Guinea, Hungary, Iran, Lebanon, Mongolia, Myanmar, Nicaragua, Pakistan, Paraguay, Serbia, Tunisia, Turkmenistan, UAE, Venezuela, West Bank	11-Aug-2020
Convidecia (Ad5-nCoV)	CanSino Biologics (China)	Inactivated vaccine	A form of the virus that has been inactivated or weakened so it does not cause disease, but still generates an immune response	Emergency use	Mexico China	Jun-2020
EpiVacCorona	Vector Institute (Russia)	Peptide vaccine	Uses fragments of proteins or protein shells that mimic the COVID-19 virus to safely generate an immune response	Early Use	Russia	14-Oct-2020
BBIBP-CorV	Beijing Institute of Biological Products/Sinopharm (China)	Inactivated vaccine	A form of the virus that has been inactivated or weakened so it does not cause disease, but still generates an immune response	Approved Emergency Use	China Bahrain, Cambodia, Egypt, Hungary, Iraq, Jordan, Morocco, Pakistan, Peru, Serbia, Seychelles, UAE	05-Jan-2021
Corona Vac (PiCo Vacc)	Sinovac Biotech (China)	Inactivated vaccine		Approved Emergency Use	China Brazil, Chile, Colombia, Indonesia, Mexico, Turkey	08-Feb -2021
Unnamed	Sinopharm/Wuhan Institute of Biological Products (China)	Inactivated vaccine		Approved	UAE, Bahrain China	09-Dec-2020 30-Dec-2020
Covaxin (BBV152A, B, C)	Bharat Biotech, Indian Council of Medical Research, National Institutes of Virology	Inactivated vaccine		Emergency Use	India	03-Jan-2021
Kovivac	Chumakov Center	Inactivated vaccine		Early Use	Russia	20-Feb-2021
QazCovid-in/QazVac	Kazakhstan Research Institute for Biological Safety Problems (RIBSP)	Inactivated vaccine		Early Use	Kazakhstan	28-Apr-2021
Anhui Zhifei Longcom: RBD-Dimer (ZF2001)	Anhui Zhifei Longcom and Institute of Medical Biology at the Chinese Academy of Medical Sciences	Protein subunit-based vaccine with adjuvant	Uses part of the COVID-19 virus (S protein) to generate an immune response	Emergency Use	Uzbekistan China	01-Mar-2021 15-Mar-2021

or flexible clinical programs, the regulators would expect to see a combination of early clinical study phases together, so that Phase I first-in-human trials are often paired with early Phase II as a proof of concept or efficacy studies, or later Phase II studies could be integrated with the final pre-approval phase (Phase III) in some cases. Furthermore, studies within a single phase of development could include in-study decisions/options based on review of interim data by the regulator as an alternative to flexible trial design.

However, the concept of a complete combined clinical program spanning the initial Phase I safety testing through to Phase II and even further beyond to the large scale, multinational Phase III confirmatory studies, is something that has not routinely been experienced pre-SARS-CoV-2 vaccine development, demonstrating the wider extent to which existing regulatory strategies have been tested by the developers of SARS-CoV-2 vaccines. All the SARS-CoV-2 vaccines authorized to date have taken this combined development approach, initiating large multi-phase studies with many points of interim analysis and real-time data review by the regulators, taking the concept of rolling data reviews and adaptive study designs to their very limits. In doing so, the developers have demonstrated that the successful development of a vaccine (or any other future medicine) is possible using this approach, so long as the trials are appropriately designed, endpoints, safety measurements, and stopping criteria should the trial encounter any safety issues, are all well defined. Similarly, the regulators have successfully demonstrated that they can regulate a new vaccine with a more streamlined, adaptive, and pragmatic method, and this could potentially be extrapolated to other new medicines in the future. Therefore, it is possible that in light of the successful SARS-CoV-2 vaccine authorizations, what may change, or at the very least be re-considered in some circumstances, is the traditional rigidity of regulations that follow a very defined and sequential route with mandatory stage-gate requirements before proceeding to the next stage.

It is clear that in response to evolving technologies or changes to the way patients have access to new medicines, a traditional route to approval is not always the most efficient. However, it is important to note that all the SARS-CoV-2 vaccines to date are conditionally authorized for use in this emergency and are not yet fully approved or licensed, and thus they are all subject to additional data being generated by the developer and reviewed by the regulator. Therefore, although adaptive designs may become more widely accepted by regulators, the speed of future reviews and approvals may not entirely mimic the speed of the SARS-CoV-2 vaccine reviews. For example, a possible future adaptation of the extremely flexible approach could be that multi-combined phase designs become routinely accepted, but unlike the SARS-CoV-2 vaccines, all the interim analysis and data must be fully generated, reviewed, and finalized before moving to the next development stage. Additionally, future adaptive designs may still need to fulfill the traditional regulatory requirements of specific data being available at the point of submission, rather than post-submission (unless, of course, it is another conditional

approval strategy).

It is therefore possible to see a change in regulation on how clinical development programs are designed, and regulatory strategies defined. But it is also fair to assume that where SARS-CoV-2 vaccine development has paved the way for this extremely efficient, streamlined, and real-time adaptive approach, it will only be elements of this approach that may be carried forward on a large scale, routine basis.

7. Is It Too Soon to Decide Whether a Change in Regulation is Possible?

There are many learnings to be taken from the successful development of SARS-CoV-2 vaccines, and how regulators have approached authorization of these products; however, it is too early to decide whether a change in future regulation is possible.

While the developers of SARS-CoV-2 vaccines working collaboratively with the regulators have provided many good examples of how utilizing existing pragmatic regulatory strategies to their full extent could be the future change in regulation, there is certainly no complete end-to-end picture of development yet. None of the vaccines authorized for use have been fully licensed and are all subject to additional data generation and further review before full license becomes a realistic possibility. To understand whether the strategies employed by SARS-CoV-2 vaccine developers have truly changed the way future medicines may be regulated, it may be prudent to wait until such vaccines have been fully licensed following the provision of all of the required data and follow-up activities prescribed by the regulator. It is only then, when a full picture of the entire regulatory process for the SARS-CoV-2 vaccines is available, that a conclusion may be drawn.

8. Changing Regulatory Perspectives

Many positive learnings may be taken from the regulation of SARS-CoV-2 vaccines to date. Developers and regulators have demonstrated their ability to adapt to an incredibly challenging and ever-evolving situation, with regulators proving that pragmatism could be key to the successful development of urgently needed medicines. Although regulators may more widely adapt the concept of pragmatism in their future review of new medicines, it must be noted that this is no excuse for reduced data, a lesser need to demonstrate safety, quality, and efficacy, nor is it an excuse to lower the regulatory hurdles where not warranted. Regulatory requirements, particularly in International Conference on Harmonization members, have been developed carefully over a number of years to ensure medicines are consistently developed safely, to an appropriately defined quality standard, and are efficacious for the end user.

Another element of change that may be embedded in future regulation is the stronger collaborations and relationships between the developers and the regulator. Where historically there may have been differences in goals, with the regulator and the

developer often on perceived opposing sides, there is no doubt that there is a huge potential for a widespread change in this mindset. As a result of this common goal or shared vision, the role of the regulator may be perceived differently now. Prior to COVID-19 many have traditionally considered the regulator as a barrier to commercialization and although all would acknowledge the need and importance of this barrier, many developers would still recount difficulties and inflexibilities during regulatory review, with consequential delays or changes to development strategies. However, it is fair to conclude that as a direct consequence of how the SARS-CoV-2 vaccines have been reviewed, this perception may have completely changed for the better.

It is also likely that the voice and presence of the regulator will change following COVID-19. Previously, internal regulatory affairs departments as well as the external regulators were a relatively niche entity, with many in the industry not having a full appreciation of the intricacies or skill required to successfully navigate this hugely influential part of the development process. The importance of a skilled and pragmatic regulatory team capable of generating an appropriate and creative regulatory strategy is greater than ever before, with successful product approval depending largely on the skill of the regulatory affairs department that is responsible for preparing and presenting the information package to the regulator for review.

9. Conclusion

There is no doubt that COVID-19 has changed many aspects of normal life, and while most of these may be considered a disadvantage or detrimental, one sure success of the pandemic is the demonstrated ability to design, develop, manufacture, and regulate novel vaccines in rapid time. The role of the regulator in this huge success story is unquestionable and has presented new possibilities to shape the future of regulating medicines. The way in which the regulator may employ pragmatic approaches to review, the real-time collaboration and interaction with the developer or simply the acceptance of a change to traditional regulation may all contribute to a future change. Where many can agree the replication of the SARS-CoV-2 vaccine regulation approach is not scalable or even necessary for all development programs, surely all can agree that the pragmatism, flexibility, and adaptivity to change shown by regulators are certainly elements that could and should be adopted for future regulation to some extent or another.

Traditional regulation, with strict definitions for program development and data requirements, has been the kingpin in ensuring patients receive safe and effective medicines for many decades. However, with the radical changes in the type of medicines available over recent years, it is clear that traditional development routes may need to change to accommodate these novel products. Therefore, where there was no clear path previously in how to successfully achieve this change, the COVID-19 pandemic and subsequent vaccine development may well have demonstrated a potential solution to this need

for change.

10. Article Information

This article was received February 17, 2021, in revised form May 17, 2021, and made available online July 14, 2021.

11. References

- [1] UK Statutory Instruments. (2012). *The Human Medicines Regulations 2012*. (No.1916 Part 10). Retrieved February 15, 2021 from <https://www.legislation.gov.uk/ukxi/2012/1916/contents/made>
- [2] Medicines & Healthcare products Regulatory Agency. (2020). *Conditions of Authorisations for Pfizer/BioNTech COVID-19 vaccine*. Retrieved February 15, 2021 from <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/conditions-of-authorisation-for-pfizerbiontech-covid-19-vaccine>
- [3] United States Food & Drug Administration. (2017, January). *Emergency Use Authorization of Medical Products and Related Authorities*. Retrieved February 15, 2021 from <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities>
- [4] COVID-19 Vaccine Tracker. (n.d.). *Vaccines – COVID19 Vaccine Tracker*. Retrieved February 15, 2021 from <https://covid19.trackvaccines.org/vaccines/>
- [5] United States Food & Drug Administration. (2021) *Pfizer-BioNTech COVID-19 Vaccine*. Retrieved February 15, 2021 <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine>
- [6] European Medicines Agency. (2020). *Comirnaty*. Retrieved February 15, 2021 from <https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty>
- [7] UK Department of Health and Social Care & Medicines & Healthcare products Regulatory Agency. (n.d.). *Reg 174 Information for UK Healthcare Professionals*. Retrieved February 15, 2021 from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/997050/Temporary_Authorisation_HCP_Information_BNT162_12_0_UK_clean.pdf
- [8] Townsen, K. & Stockton, L. L. P. (2021, January 11). *The Lead COVID-19 Vaccine Candidates: Where We Are and What You Should Know*. Retrieved February 15, 2021 from <https://www.kilpatricktownsend.com/Blog/MEMO/2021/1/The-Lead-COVID-19-Vaccine-Candidates—Where-We-Are-and-What-You-Should-Know>
- [9] Zimmer, C., Corum, J. & Wee, S. L. (2021). *Coronavirus Vaccine Tracker*. Retrieved February 15, 2021 from <https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html>