Can the COVID-19 Pandemic Disrupt the Current Drug Development Practices?

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Abstract: Therapeutics and vaccines against the COVID-19 pandemic need to be developed rapidly and efficiently, given its severity. To maximize the efficiency and productivity of drug development, the world has adopted disruptive technologies and approaches in various drug development areas. Telehealth, characterized by the heavy use of digital technologies; drug repositioning strategies, aided by computational breakthroughs; and data tracking tool hubs, enabling real-time information sharing, have received much attention. Moreover, drug developers have engaged in open innovation by establishing various types of collaborations, many of which have been carried out across nations and enterprises. Finally, regulatory agencies have attempted to operate on a more flexible review basis than before. Although such disruptive approaches have partly reshaped drug development practices, issues and challenges remain before the completion of this paradigm shift in conventional drug development practices for the post-pandemic era. In this review, we have highlighted the role of a collaborative community of experts in order to figure out how disruptive technologies can be fully integrated into the current drug development practices and improve drug development efficiency for the post-pandemic era.

Keywords: COVID-19; drug development; paradigm shift

1. Introduction

Drug development is a complex, lengthy, costly process. It takes more than 10 years from the discovery of a drug candidate for it to attain regulatory approval. Furthermore, the average cost of developing a new drug is 1.3 billion US dollars [1]. However, in a global health crisis such as the coronavirus disease 2019 (COVID-19) pandemic, in which treatments and preventive vaccines must be developed rapidly and efficiently to avert the pandemic, mounting costs and lengthy processes are certainly not welcomed.

The response to the COVID-19 pandemic at an unprecedented global scale has started shifting the old paradigm of drug development to improve the efficiency and productivity of drug research and development in the post-pandemic era. For example, ‘telehealth’ or non-face-to-face health care practices, involving the heavy use of digital technology, has received much attention [2]. Furthermore, scientists have applied artificial intelligence (AI) technologies to screening drug candidates to increase the success rate of the drug repositioning strategy. Engineers have also invented data tracking tools and data hubs to collect and share the development status of drug candidates and to update the results of
In addition, more and more public-private collaborations, many of which have occurred across the nations and enterprises, have been actively pursued. Furthermore, partly in response to the unavoidable challenges and changes in drug development, regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have tried to operate on a more flexible basis, while not undermining the scientific foundation of the drug review process.

The objectives of this review were threefold. First, we describe how the COVID-19 pandemic has disrupted the previous paradigm of drug development. Second, we anticipate how those disruptions could further reshape and transform drug development practices in the future, particularly for clinical development. Lastly, we discuss the issues and challenges in this transition, and how those roadblocks could be overcome.

2. Wide Acceptance of Telehealth

‘Telehealth’ is a type of health care in which information and communication technologies (ICT) play an indispensable role in delivering medical services to patients [4]. Telehealth is a complex term that covers a broad range of specialties and health-related services. Virtual visits and remote video monitoring are examples of telehealth [4].

Telehealth can minimize the possibility of transmitting infections between patients and health care providers. Therefore, the COVID-19 pandemic has hugely encouraged the adoption of telehealth. Compared with pre-COVID-19, health care providers are now seeing 50 to 175 times the number of patients via telehealth [2]. Clinicians have used telehealth to screen patients for COVID-19 using a heat detection device [2]. Likewise, doctors have monitored patients remotely and provided medical advice for quarantined patients or patients who are located in isolated areas, where access to medical services is limited [2,5].

Traditionally, clinical trials were performed at clinics and hospitals, thereby mandating patient visits and face-to-face on-site encounters between patients and healthcare providers. However, the COVID-19 pandemic has prompted the extensive adoption of decentralized clinical trials (DCTs), which are defined as clinical trials executed through telehealth technologies such as biosensors, wireless communication systems, and remote video monitoring [6,7]. For example, in a clinical trial to evaluate the efficacy and the safety of hydroxychloroquine to treat patients with COVID-19 infection (NCT04308668), participants and clinicians communicated via e-mails or text messages, without on-site visits [6]. This study also used commercial couriers to deliver the investigational drugs, i.e., hydroxychloroquine or placebos, to the study participants [6]. Patients’ visits to clinics can be minimized in DCTs using telehealth technologies. Thus, DCTs can reduce the patient’s burden in scheduling and traveling for clinic visits, and have the potential to improve patient retention rates in clinical trials, which eventually helps in patient recruitment. Likewise, DCTs using telehealth technologies can overcome geographical obstacles, expanding the access to clinical trials on a global scale, which was impractical and cumbersome, if not impossible, in traditional clinical trials.

Despite these benefits, telehealth may not be appropriate for all types of clinical trials [8]. For example, early-phase clinical trials to find the maximum tolerated dose of a drug candidate require frequent interventions, such as dose modifications, carried out by closely monitoring study participants, preferably in a confined area. Traditional designs are better suited for early-phase clinical trials because they need staffing capabilities and centralized resources. On the other hand, the lack of adequate ICT infrastructure may make it difficult to handle massive amounts of data coming from various telehealth devices [4,9]. Moreover, the lack of legislation and reimbursement mechanisms specific to telehealth are additional challenges in the wider use of telehealth [10,11]. To ensure that telehealth-based clinical trials are practical, safe, and efficient, both drug developers and engineers should actively validate telehealth technologies and publicly report their findings. The pharmaceutical industry has also raised concerns about unclear regulatory acceptance, noting that regulators are not fully ready to accept clinical endpoints reported
mainly through telehealth devices. For example, twelve countries in the Organization for Economic Co-operation and Development (OECD) still have no national legislation on how to implement and manage telehealth services, although they have legalized the use of telehealth [9]. Because telehealth is a complex term requiring a wide range of specialties [4,9], securing a cross-disciplinary team, which consists of clinicians, health care providers, policy makers, and engineers of telehealth technologies, is crucial in developing standardized legislation specific to telehealth.

3. Drug Repositioning Revisited

Drug repositioning helps identify new therapeutic uses of an investigational or approved drug [12]. Drug repositioning could save time and expenses in drug development because the safety of repositioned drugs has already been tested in preclinical studies or clinical trials, though not completely [12]. In the COVID-19 pandemic, in which time is of the essence, drug repositioning has received attention in order to develop treatments and vaccines against SARS-CoV-2 at a much faster rate than before.

Typical drug repositioning consists of three steps: identifying repositionable candidates, assessing their effects in preclinical models, and evaluating their efficacy and safety in clinical trials. Traditionally, retrospective pharmacological analysis, performed mostly in a haphazard and non-systematic manner, has been used to identify repositionable candidates [13]. For example, sildenafil citrate was unexpectedly found to be effective for erectile dysfunction in clinical trials evaluating the efficacy of sildenafil as an angina treatment [13]. Furthermore, repositioning of thalidomide for erythema nodosum leprosum and multiple myeloma [14], aspirin for colorectal cancer [15], and raloxifene for breast cancer relied on empirical clinical experience and/or pharmacological analyses [16]. Likewise, in the early phase of the COVID-19 pandemic, several antiviral drugs such as remdesivir [17–19], chloroquine [20–22], and lopinavir/ritonavir [23,24], which showed broad-spectrum antiviral activity in several preclinical or clinical studies, had been repositioned for COVID-19 treatment [25]. However, few of those drugs repositioned against SARS-CoV-2 have shown satisfactory clinical efficacy [25].

To overcome the pitfalls of trial-and-error drug repositioning, researchers have searched for other approaches, of which AI is an example (Table 1) [13,26–32]. For instance, researchers from the US and Korea invented the Molecule Transformer-Drug Target Interaction deep learning model to identify repositionable antiviral candidates against SARS-CoV-2 [33]. Furthermore, to confirm the performance of the model, researchers compared the binding affinities of repositioned drugs against SARS-CoV-2 with FDA-approved drugs using AutoDock Vina, which is a widely used software for 3D-structure based docking and virtual screening [33]. Moreover, researchers and engineers from the Technical University of Munich have developed CoVex, a network medicine online platform that integrates published data about virus–human protein interactions, human protein–protein interactions and drug–target interactions for SARS-CoV-2 into a large-scale interactome [34]. CoVex platform users can systematically identify repositionable drugs against SARS-CoV-2 by mining the integrated virus–host–drug interactome [34,35]. In addition, the developers of CoVex have planned to extend the platform to other viruses, including influenza, Dengue fever, MERS, and Zika [34]. Likewise, an AI platform established by the National Health Research Institute in Taiwan identified eighty repositionable approved drugs targeting SARS-CoV-2. Among them, eight drugs (i.e., vismodegib, gencitabine, clofazimine, celecoxib, brequinar, conivaptan, bedaquiline, and tolcapone) showed antiviral activities against the feline coronavirus in an in vitro cell-based assay [36]. Furthermore, using its AI platform and biomedical knowledge graph, BenevolentAI, a global company involved in the development and application of AI and computational medicine technologies, identified baricitinib, an oral Janus kinase (JAK) inhibitor, as a promising repositionable treatment against SARS-CoV-2 [30–32]. Eli Lily, who owns baricitinib, launched the Adaptive COVID-19 Treatment Trial (ACTT-2, n = 1034, NCT04401579), in which the combination of baricitinib and remdesivir was found to reduce recovery time and progres-
sion to ventilation or death compared to remdesivir alone in COVID-19 patients in clinical status [37,38]. Based on the results of ACTT-2, on 19 November, 2020, the US FDA granted an Emergency Use Authorization (EUA) for baricitinib in combination with remdesivir, for the treatment of hospitalized COVID-19 adults and pediatric patients (2 years of age or older), who require invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [39]. Although computational-technology-aided drug repositioning strategies are in the nascent stage, this approach has shown the potential to be developed into a promising alternative to the current empirical drug repositioning methodology [25,40].

Table 1. Computational-technology-aided drug repositioning strategies used to identify repositionable drugs for SARS-CoV-2.

| Methods or Models | Data or Software Used | Identified Repositionable Drugs for SARS-CoV-2 | References |
|-------------------|-----------------------|----------------------------------------------|------------|
| MT-DTI Deep Learning Model | NCBI Database, DTC Database, BindingDB Database, DrugBank Database (SMILES) | Atazanavir, Remdesivir, Kaletra, Rapamycin, Tiotropium Bromide | [33] |
| Deep Neural Network Model | DrugBank Database (Data of Approved Drugs and 3C-Like Protease Inhibitors) | Bedaquiline, Brequinar, Celecoxib, Clofazimine, Conivaptan, Gemiclабine, Tocapone, Vismodegib | [36] |
| Pharmacology-Based Network Model | NCBI GenBank Database, EMBL-EBI database, DrugBank Database (SMILES), Therapeutic Target Database, PharmGKB Database, ChemBL, BindingDB, IUPHAR/BPS Guide to PHARMACOLOGY90, UniProt Database | Imbesartan, Toremifene, Camphor, Equilin, Mesalazine, Mercaptopurine, Paroxetine, Sirolimus, Carvedilol, Colchicine, Daclomycin, Melatonin, Quinacrine, Eplerenone, Emodin, Oxymetholone | [28] |
| Hierarchical Virtual Screening (MMFF-Based Free Energy Calculation Methods) | Schrodinger Software, OpenBabel Software, AMBER Software (Molecular Dynamics Simulation), DrugBank Database (DTIs) | Carfilzomib, Enarvacycline, Valrubicin, Lopinavir, Elbasvir, Streptomycin | [29] |
| BenevolentAI Platform (MCTS algorithm and Deep Neural Network Model) | Reaxys Chemistry Database, ZINC Database | Baracitinib, Fedratinib, Sunitinib, Erlotinib | [30–32] |
| Physics-Based Glide Algorithm | Schrodinger Software, Broad Repurposing Library, Biotek Gen5 Software, GraphPad Prism 8 | Boceprevir, Ciluprevir, Narlaprevir, Telaprevir | [41] |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MT-DTI, molecule transformer–drug target interaction; NCBI, National Center for Biotechnology Information; DTC, Drug Target Commons; SMILES, Simplified Molecular-Input Line-Entry System; AI, artificial intelligence; MMFF, molecular mechanical force field; DTI, drug–drug target interaction; MCTS, Monte Carlo tree search.

4. Real-Time Information Sharing: Data Tracking Tools and Hubs

As the severity of the COVID-19 pandemic has escalated, studies to evaluate the efficacy and safety of treatments and vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are being conducted at an unparalleled speed. For example, as of 19 March 2021, a total of 2803 clinical trials of COVID-19 treatments are being conducted worldwide [42]. Given the rapid speed at which the results of those clinical trials are updated, engineers have created data tracking tools to enumerate and identify the development status of the drug candidates and to update the results of their clinical trials. For example, Cytel, a multinational statistical software developer, developed an AI-based tracking tool to aggregate clinical trial data related to COVID-19 [3,42,43]. The tool pulls data from ClinicalTrials.gov, the Chinese Clinical Trial Registry, the EU Clinical Trials Register, Clinical Research Information Service (South Korea), International Standard Randomised Controlled Trial Number (ISRCTN), the Iranian Registry of Clinical Trials, the Japan Primary Registries Network, and the German Clinical Trials Register [3]. Cytel also built a real-time dashboard, a web portal that provides the overview of the global clinical trials of COVID-19 [42]. In addition, medical journals such as The New England Journal of Medicine [44], The BMJ [45], and The Lancet [46], have provided a data hub that shares trial reports, latest news, practical guidelines, and commentary about the COVID-19 pandemic. On the other hand, the state government of Georgia, US, has daily updated and provided
geospatial analyses (e.g., Georgia’s COVID-19 case summary, death data summary, and maps of regional hospital capacity) via its COVID-19 data hub, using data pooled from labs, hospitals, and health care providers [47]. Data tracking tools and data hubs have provided researchers with various COVID-19-specific forms of content, especially timely information and updates regarding clinical trials. This has eventually allowed researchers to avoid duplicating efforts and expenses by screening out existing or active clinical research [3].

5. Public–Private Collaborations Expanded

Historically, drug development has been led by distinct players, with minimal collaboration between them. Biopharmaceutical companies, academia, and the National Institutes of Health (NIH) in the US or similar government-funded research organizations in other countries have worked independently with different goals, processes, and success criteria [48]. Likewise, individual pharmaceutical companies competed with each other to gain the upper hand in the drug market. Therefore, little to no collaboration was successfully pursued in the old era of drug development.

However, the COVID-19 pandemic has changed the situation. In the midst of the pandemic, academia, nonprofit organizations, governments, and biopharmaceutical companies avidly opened up collaborations with each other to address the public health crisis at a global scale. For example, the US NIH established ‘Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)’, a public–private partnership, which consists of academia, government agencies (e.g., the US FDA), non-profit organizations (e.g., the Bill and Melinda Gates Foundation), and industry (i.e., twenty pharmaceutical companies) [49]. ACTIV aims to accelerate COVID-19 drug development by efficiently utilizing limited biomedical resources and prioritizing the most promising vaccine candidates against SARS-CoV-2 [49]. Moreover, governments around the world have joined the COVAX Facility, a global risk-sharing mechanism for COVID-19 vaccines [50]. The COVAX Facility, co-led by the World Health Organization (WHO), the Infectious Diseases Innovation Association (CEPI), and the World Vaccine Immunity Association (GAVI), aims to provide an equal supply of vaccines to at least 20% of the world’s population [50].

Biopharmaceutical companies have also actively formed partnerships between themselves, many of which have occurred across nations and enterprises (Table 2). For example, CSL Behring and Takeda co-founded the ‘CoVig-19 Plasma Alliance’, which includes leading global plasma companies (i.e., Biopharm Plasma, Biotest, GC Pharma, Octapharma, LFB, NBI, and Sanquin) [51]. The CoVig-19 Plasma Alliance, supported by the National Institute of Allergy and Infectious Diseases (NIAID), NIH, US, has been developing hyperimmune globulin (H-Ig), a non-branded plasma-derived medicine for COVID-19 [51]. Furthermore, a French biopharmaceutical company, Sanofi, and an English biopharmaceutical company, GlaxoSmithKline (GSK), combined their innovative technologies to effectively develop a COVID-19 vaccine [52]. Based on Sanofi’s DNA recombination technology, Sanofi has contributed to producing the spike protein of SARS-CoV-2 [52]. On the other hand, GSK, which has a vaccine portfolio of more than twenty diseases [53], has contributed its proven adjuvant technology to reduce the amount of vaccine protein required per dose [52]. Furthermore, the American pharmaceutical company Pfizer and the German biotechnology company BioNTech co-developed BNT162, an mRNA COVID-19 vaccine [54]. Likewise, Moderna, a Boston-based company, developed an mRNA-1273 vaccine in collaboration with the NIAID, NIH, US [55]. In addition, AstraZeneca, a British–Swedish pharmaceutical company, collaborated with the University of Oxford to advance basic vaccinology research [56]. Through collaboration, pharmaceutical companies have been able to access external know-how and knowledge and have also been able to maximize the returns on their research and development. As a result of these monumental and innovative collaborations, vaccines against SARS-CoV-2 are being developed at an unrivalled pace [57]. As of 16 April, 2021, a total of 13 COVID-19 vaccine candidates have received regulatory approvals in the world for full or limited use (Table 3) [57,58].
Table 2. COVID-19 vaccines and partnerships [57,58].

| Product                          | Developer | In Partnership with                                      |
|----------------------------------|-----------|---------------------------------------------------------|
| Ad26.COV2.S                      | Johnson & Johnson | Beth Israel Deaconess Medical Center                    |
| AG0302-COVID19                   | AnGes     | Osaka University and Takara Bio                         |
| ARCoV                            | Academy of Military Medical Sciences | Suzhou Abogen Biosciences and Walvax Biotechnology       |
| Ad5 and Ad35                     | Cellid    | LG Chem                                                 |
| Comirnaty                        | Pfizer    | BioNTech                                                |
| Convidecia                       | CanSino Biologics | Academy of Military Medical Sciences                    |
| Covaxin                          | Bharat Biotech | Indian Council of Medical Research and the National Institute of Virology |
| COVID-19 viral protein           | Sanofi    | GSK                                                     |
| CoVLP                            | Medicago  | GSK                                                     |
| ChulaCov19                       | Chulalongkorn University | Chula Vaccine Research Center                          |
| DS-5670                          | Daiichi Sankyo | University of Tokyo                                    |
| GBP510                           | University of Washington | SK Bioscience and GSK                                   |
| GRAd-COV2                        | ReiThera  | Lazzaro Spallanzani National Institute for Infectious Diseases |
| HGC019                           | Gennova Biopharmaceuticals | HDT Bio                                               |
| mRNA-1273                        | Moderna   | NIH                                                     |
| mRNA Vaccine                     | Arcturus Therapeutics | Duke-NUS Medical School                                |
| S Protein of COVID-19            | Clover Biopharmaceuticals | Dynavax.                                               |
| Vaxzevria                        | University of Oxford | AstraZeneca                                           |
| ZF2001                           | Anhui Zhifei Longcom | The Institute of Medical Biology at the Chinese Academy of Medical Sciences |

Updated 16 April, 2021. Data from The New York Times, based on reports from state and local health agencies. COVID-19, coronavirus disease 2019; NIH, National Institutes of Health; GSK, GalxoSmithKline.

Table 3. Current approval status of COVID-19 vaccines [57,58].

| Developer                        | Product | Approved for Full Use in                                      | Approved for Emergency or Early Use in                                      |
|----------------------------------|---------|----------------------------------------------------------------|---------------------------------------------------------------------------|
| Pfizer and BioNTech              | Comirnaty | Bahrain, Brazil, New Zealand, Saudi Arabia, Switzerland           | US, EU, UK, Argentina, Australia, Botswana, Canada, Costa Rica, Greenland, Hong Kong, Iceland, Iraq, Japan, Kuwait, Lebanon, Mexico, Norway, Panama, Peru, South Africa, South Korea, Thailand, Turkey, UAE, other countries |
| Moderna                          | mRNA-1273 | Switzerland                                                  | US, EU, UK, Canada, Greenland, Iceland, Israel, Mongolia, Norway, Qatar, Singapore, Thailand, Vietnam |
| Johnson & Johnson                | Ad26.COV2.S | Not Approved                                               | US, EU, Brazil, Canada, Colombia, Greenland, Iceland, Liechtenstein, Norway, South Africa, South Korea, Switzerland, Thailand |
| Oxford and AstraZeneca           | Vaxzevria | Brazil                                                      | EU, UK, Algeria, Argentina, Australia, Bahamas, Brazil, Brunei, Canada, Chile, Colombia, Dominican Republic, Egypt, El Salvador, Greenland, Hungary, Iceland, Mexico, Namibia, Sri Lanka, South Africa, South Korea, Vietnam, other countries |
| Gamaleya Research Institute      | Sputnik V | Not Approved                                               | Russia, Algeria, Argentina, Bahrain, Bosnian Serb Republic, Cameroon, Congo Republic, Djibouti, Egypt, Hungary, Honduras, Iran, Iraq, Jordan, Laos, Lebanon, Mali, Morocco, North Macedonia, Paraguay, Palestinian Authority, Philippines, Sri Lanka, UAE, other countries |
Table 3. Cont.

| Developer               | Product         | Approved for Full Use in | Approved for Emergency or Early Use in |
|-------------------------|-----------------|--------------------------|----------------------------------------|
| Sinovac                 | CoronaVac       | China                    | Azerbaijan, Brazil, Cambodia, Chile, Colombia, Ecuador, Hong Kong, Indonesia, Laos, Malaysia, Mexico, Pakistan, Panama, Philippines, Thailand, Tunisia, Turkey, Ukraine, Uruguay, Zimbabwe |
| Sinopharm (Beijing)     | BBIBP-CorV      | Bahrain, China, UAE      | Argentina, Brunei, Cambodia, Egypt, Gabon, Guyana, Hungary, Iran, Iraq, Jordan, Maldives, Namibia, Nepal, Pakistan, Peru, Venezuela, Zimbabwe |
| FBRI                    | EpiVacCorona    | Turkmenistan             | Russia                                 |
| Chumakov Center         | KoviiVac        | Not Approved             | Russia                                 |
| CanSino Biologics        | Convídecia      | China                    | Chile, Hungary, Mexico, Pakistan       |
| Bharat Biotech          | Covaxin         | Not Approved             | India                                  |
| Anhui Zhifei Longcom    | ZF2001          | Not Approved             | China, Uzbekistan                      |

Updated 16 April, 2021. Data from The New York Times, based on reports from state and local health agencies. COVID-19, coronavirus disease 2019; US, United States; EU, European Union; UK, United Kingdom; UAE, United Arab Emirates.

Because vaccine manufacturing under good manufacturing practices (GMPs) is a highly complex process and requires substantial financial investments [59], various partnerships between vaccine developers and manufacturers have been established to enable the scaled-up production of those COVID-19 vaccines under GMPs [60]. For example, South Korea’s biopharmaceutical company SK Bioscience signed a contract manufacturing organization (CMO) deal and a contract development and manufacturing organization (CDMO) deal with AstraZeneca [61] and Novavax [62], respectively. SK Bioscience will produce up to 500 million doses of AstraZeneca’s COVID-19 vaccine and 40 million doses of Novavax’s COVID-19 vaccine [61,63]. Likewise, Moderna has made a 10-year strategic agreement with Lonza, a Swiss multinational chemicals and biotechnology company [64]. The purpose of the agreement was to enable the manufacturing of up to 1 billion doses of mRNA-1273 per year, as well as to prepare for the future manufacturing of additional products in Moderna’s extensive clinical portfolio [64].

The COVID-19 pandemic has prompted various types of collaborations to increase the efficiency of drug development and to avert the global pandemic. The present is the most opportune time to set aside individualism and to adopt open approaches more actively for ground-breaking drug research and development.

6. Changes and Challenges in the Regulatory Agencies

Historically, strict regulations, inflexible procedures, and time-consuming review processes by regulatory agencies have been criticized for delayed marketing approvals of drugs [65]. However, the COVID-19 pandemic has prompted the regulatory agencies to operate on more simplified and flexible administrative procedures and review bases than before, while not undermining the scientific foundation of drug review.

Many regulatory agencies have established emergency taskforces or programs to support drug developers and to take prompt regulatory actions [66,67]. For example, the EMA has established the COVID-19 EMA pandemic taskforce (COVID-ETF) and the EMA COVID-19 steering group to preemptively address possible delays in the review of COVID-19 treatments and vaccines, as well as for non-COVID-19-related assessments [67]. COVID-ETF provides scientific support and feedback for drug developers to expedite clinical trials and development plans for COVID-19 medicines [67,68]. The EMA COVID-19 steering group has not only coordinated the activities of COVID-ETF, but has also revised the procedures to introduce more flexibility for the fast-tracked approval of medicines [67]. Similarly, the FDA has accepted data from diverse sources in regulatory decision-making to
combat the COVID-19 pandemic, even if the data were not obtained from clinical trials. In June 2020, the FDA, in a collaboration with the NIH, formed the CURE Drug Repurposing Collaboratory (CDRC), a partnership that initiated the COVID-19 pilot program to collect real-world data for identifying potential treatments for SARS-CoV-2 [66]. CDRC has utilized real-world data to support and power randomized clinical trials in which it was difficult to enroll a sufficient number of COVID-19 patients [66,69].

Thirteen years ago, PricewaterhouseCoopers (PwC), a multinational management consulting firm, anticipated that by 2020 regulators would grant limited marketing approval based on ‘live licenses’, which are conditional approvals in a restricted patient populations and/or with a narrow indication for further in-life-testing to evaluate long-term safety and efficacy in various populations [70]. These predictions have proved to be correct, as the US FDA and the EMA have granted many EUAs to address the need for diagnostic kits, treatments, and vaccines for COVID-19 in a timely manner. EUAs do not constitute full regulatory approval, which typically requires the submission of substantial evidence for the safety and efficacy of a drug, diagnostic kit, or medical device [39]. In a public health crisis such as the COVID-19 pandemic, however, the regulatory agencies had to balance the unquestionable long-term safety and efficacy of the vaccines or treatments and the urgent need for them by the public. Stephen M. Hahn, the US FDA Commissioner, has stressed that, in a situation where the two demands conflict, the regulatory agencies should consider granting an EUA if the risks of not having treatments or vaccines are much greater than the risks associated with the products themselves [71].

However, the public has raised concerns about the scientific rigor and transparency of the EUA process. On 28 March, 2020, without disclosing the evidence underlying the decision, the US FDA granted an EUA for the use of hydroxychloroquine for the treatment of COVID-19 [71,72]. Not long afterwards, on 15 June, 2020, the US FDA revoked an EUA of hydroxychloroquine, noting that hydroxychloroquine was not effective in reducing mortality or in speeding up the recovery of COVID-19 patients [73]. Such erroneous and poor decision-making has reduced the credibility and public confidence in regulatory agencies’ decisions [74]. Kyle Thomson, the FDA’s Chief Counsel from 2012 to 2020, emphasized that regulatory agencies should clarify evidence standards for EUAs [71]. Additional clarity and transparency in EUA standards and processes will increase the consistency and quality of regulatory agencies’ decisions on EUAs, thereby increasing the trust and confidence of the public [71,74].

7. Conclusions

The COVID-19 pandemic has encouraged the adoption of disruptive approaches in various areas of drug development. For example, telehealth, strengthened by the heavy use of digital technologies and data tracking tools that enable real-time information sharing, have increased the efficiency and practicality of clinical trials in terms of trial conduct and patient enrollment. Likewise, computational breakthroughs have increased the success rate of drug repositioning strategies. Furthermore, drug developers have actively adopted open innovation approaches, which are expected to increase the efficiency and productivity of drug development, and regulatory agencies have attempted to operate with more simplified and flexible administrative procedures and review methodologies than before. However, it is unclear whether these disruptions will appreciably improve the efficiency of drug development compared with conventional methods. Certainly, these disruptions could be short-lived as the public health threats by the COVID-19 pandemic vanish. Therefore, to maintain the positive effects of these disruptions, a collaborative community of experts should constantly strive to figure out how these disruptive technologies can be integrated into current drug development practices. This will, in turn, stimulate the paradigm shift in drug discovery and development created during the COVID-19 pandemic.

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23. Chan, J.F.-W.; Yao, Y.; Yeung, M.-L.; Deng, W.; Bao, L.; Jia, L.; Li, F.; Xiao, C.; Gao, H.; Yu, P. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J. Infect. Dis. 2015, 212, 1904–1913. [CrossRef] [PubMed]

24. Chan, K.; Lai, S.; Chu, C.; Tsui, E.; Tam, C.; Wong, M.; Tse, M.; Que, T.; Peiris, J.; Sung, J. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: A multicentre retrospective matched cohort study. Hong Kong Med. J. 2003, 9, 399–406. [PubMed]

25. Won, J.-H.; Lee, H. The Current Status of Drug Repositioning and Vaccine Developments for the COVID-19 Pandemic. Int. J. Mol. Sci. 2020, 21, 9775. [CrossRef]

26. Jin, G.; Wong, S.T. Toward better drug repositioning: Prioritizing and integrating existing methods into efficient pipelines. Drug Discov. Today 2014, 19, 637–644. [CrossRef]

27. Mohanty, S.; Rashid, M.H.A.; Mridul, M.; Mohanty, C.; Swayamsiddha, S. Application of Artificial Intelligence in COVID-19 drug repurposing. Diabetes Metab. Syndr. Clin. Res. Rev. 2020, 14, 1027–1031. [CrossRef]

28. Zhou, Y.; Hou, Y.; Shen, J.; Huang, Y.; Martin, W.; Cheng, F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov. 2020, 6, 1–18. [CrossRef]

29. Wang, J. Fast identification of possible drug treatment of coronavirus disease-19 (COVID-19) through computational drug repurposing study. J. Chem. Inf. Model. 2020, 60, 3277–3286. [CrossRef] [PubMed]

30. Richardson, P.; Griffin, I.; Tucker, C.; Smith, D.; Oechsle, O.; Phelan, A.; Rawling, M.; Savory, E.; Stebbing, J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020, 395, e30. [CrossRef]

31. Segler, M.H.; Preuss, M.; Waller, M.P. Planning chemical syntheses with deep neural networks and symbolic AI. Nature 2018, 555, 604–610. [CrossRef]

32. Stebbing, J.; Phelan, A.; Griffin, I.; Tucker, C.; Oechsle, O.; Smith, D.; Richardson, P. COVID-19: Combining antiviral and anti-inflammatory treatments. Lancet Infect. Dis. 2020, 20, 400–402. [CrossRef]

33. Beck, B.R.; Shin, B.; Choi, Y.; Park, S.; Kang, K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model. Comput. Struct. Biotechnol. J. 2020, 18, 784–790. [CrossRef]

34. Sadegh, S.; Matschinske, J.; Blumenthal, D.B.; Galindez, G.; Kacprowski, T.; List, M.; Nasirigerdeh, R.; Oubounyt, M.; Pichlmair, A.; Rose, T.D. Exploring the SARS-CoV-2 virus-host-drug interactome for drug repurposing. Molecules 2020, 25, 9775. [CrossRef] [PubMed]

35. Hufsky, F.; Lamkiewicz, K.; Almeida, A.; Aouacheria, A.; Arighi, C.; Bateman, A.; Baumbach, J.; Beerwenkinkel, N.; Brandt, C.; Cacciabue, M. Computational strategies to combat COVID-19: Useful tools to accelerate SARS-CoV-2 and coronavirus research. Brief. Bioinform. 2021, 22, 642–663. [CrossRef] [PubMed]

36. Ke, Y.-Y.; Peng, T.-T.; Yeh, T.-K.; Huang, W.-Z.; Chang, S.-E.; Wu, S.-H.; Hung, H.-C.; Hsu, T.-A.; Lee, S.-J.; Song, J.-S. Artificial intelligence approach fighting COVID-19 with repurposing drugs. Biomed. J. 2020, 43, 355–362. [CrossRef]

37. ClinicalTrials.gov. Adaptive COVID-19 Treatment Trial 2 (ACTT-2). Available online: https://clinicaltrials.gov/ct2/show/NCT04401579?term=baricitinib&cond=COVID&fund=0&draw=2&r.rank=2 (accessed on 20 April 2021).

38. Kalil, A.C.; Patterson, T.F.; Mehta, A.K.; Tomashek, K.M.; Wolfe, C.R.; Ghazaryan, V.; Nasirigerdeh, R.; Oubounyt, M.; Pichlmair, A.; Rose, T.D. Exploring the SARS-CoV-2 virus-host-drug interactome for drug repurposing. Molecules 2020, 25, 9775. [CrossRef] [PubMed]

39. US Food & Drug Administration. Emergency Use Authorization. Available online: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization/covidtherapeutics (accessed on 4 March 2021).

40. Romeo, I.; Mesiti, F.; Lupia, A.; Alcaro, S. Current updates on naturally occurring compounds recognizing SARS-CoV-2 druggable targets. Molecules 2021, 26, 632. [CrossRef] [PubMed]

41. Baker, J.D.; Uhrich, R.L.; Kraemer, G.C.; Love, J.E.; Kraemer, B.C. A drug repurposing screen identifies hepatitis C antivirals as inhibitors of the SARS-CoV-2 main protease. PLoS ONE 2021, 16, e0245962. [CrossRef]

42. Cytel. Global Coronavirus COVID-19 Clinical Trial Tracker. Available online: https://www.covid-trials.org/ (accessed on 7 January 2021).

43. Cytel. COVID-19: Conquering Uncertainty. Available online: https://www.cytel.com/covid19-response (accessed on 4 March 2021).

44. The New England JOURNAL of Medicine, Coronavirus (COVID-19). Available online: https://www.nejm.org/coronavirus (accessed on 4 March 2021).

45. BMJ’s Coronavirus (covid-19) Hub. Available online: https://www.bmj.com/coronavirus (accessed on 4 March 2021).

46. COVID-19 Resource Centre-The Lancet. Available online: https://www.thelancet.com/coronavirus (accessed on 4 March 2021).

47. GIO. COVID-19 Georgia Geospatial Data Hub. Available online: https://covid-hub.gio.georgia.gov/ (accessed on 19 April 2021).

48. Fishburn, C.S. Translational research: The changing landscape of drug discovery. Drug Discov. Today 2013, 18, 487–494. [CrossRef] [PubMed]

49. Collins, F.S.; Stoffels, P. Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV): An unprecedented partnership for unprecedented times. JAMA 2020, 323, 2455–2457. [CrossRef] [PubMed]
Int. J. Mol. Sci. 2021, 22, 5457

50. Gavi, T.V.A. Gavi, the Vaccine Alliance, Helps Vaccinate almost Half the World’s Children against Deadly and Debilitating Infectious Diseases. Available online: https://www.gavi.org/our-alliance/about (accessed on 19 April 2021).

51. CSL Behring. CoVig-19 Plasma Alliance Builds Strong Momentum Through Expanded Membership and Clinical Trial Collaboration. Available online: https://www.cslBehring.com/newsroom/2020/covig19-plasma-alliance-expands-membership (accessed on 19 April 2021).

52. GlaxoSmithKline. Sanofi and GSK to Join Forces in Unprecedented Vaccine Collaboration to Fight COVID-19. Available online: https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-14-13-00-00 (accessed on 19 April 2021).

53. GlaxoSmithKline. Vaccines. Available online: https://www.gsk.com/en-gb/about-us/vaccines/ (accessed on 19 April 2021).

54. Pfizer. Pfizer and Biontech Co-Develop Potential Covid-19 Vaccine. Available online: https://investors.pfizer.com/investor-news/press-release-details/2020/Pfizer-and-BioNTech-to-Co-Develop-Potential-COVID-19-Vaccine/default.aspx (accessed on 4 March 2021).

55. Moderna. Moderna’s Work on a COVID-19 Vaccine Candidate. Available online: https://www.modernatx.com/modernas-work-potential-vaccine-against-covid-19 (accessed on 4 March 2021).

56. AstraZeneca. AstraZeneca and Oxford University Announce Landmark Agreement for COVID-19 Vaccine. Available online: https://www.astrazeneca.com/content/astrazeneca/media-centre/press-releases/2020/astrazeneca-and-oxford-university-announce-landmark-agreement-for-covid-19-vaccine.html#_prclt=8mfn5tcv (accessed on 4 March 2021).

57. Denise Grady, A.E.K.; Kumar, H.; Li, C.; Tejada, C. Coronavirus Vaccine Tracker. The New York Times. Available online: https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html (accessed on 16 April 2021).

58. McGill COVID19 Vaccine Tracker Team, COVID-19 Vaccine Tracker. Available online: https://covid19.trackvaccines.org/vaccines/ (accessed on 16 April 2021).

59. Plotkin, S.; Robinson, J.M.; Cunningham, G.; Iqbal, R.; Larsen, S. The complexity and cost of vaccine manufacturing—an overview. Vaccine 2017, 35, 4064–4071. [CrossRef]

60. Media, V. Market Overview: CDMOs in the Evolving Global Vaccine Industry. Available online: https://www.pharmaceutical-technology.com/sponsored/cdmos-vaccine-industry-overview/ (accessed on 19 April 2021).

61. SK Bioscience. SK Bioscience-Ministry of Health and Welfare-AstraZeneca Signed a Trilateral Letter of Intent for Cooperation in the Global Supply of the COVID-19 Vaccine. Available online: https://www.skbioscience.co.kr/en/news/news_01_01?mode=view&i=7&page=2 (accessed on 2 April 2021).

62. SK Bioscience. SK Bioscience Signs CDMO (Contract Development and Manufacturing Organization) Agreement with US Novavax. Available online: https://www.skbioscience.co.kr/en/news/news_01_01?mode=view&i=5& (accessed on 18 April 2021).

63. SK Bioscience. SK bioscience-Novavax–KDCA Sign Licensing Agreement and Purchase Agreement for Novavax COVID-19 Vaccine Candidate. Available online: https://www.skbioscience.co.kr/en/news/news_01_01?mode=view&i=42& (accessed on 19 April 2021).

64. Moderna. Moderna and Lonza Announce Worldwide Strategic Collaboration to Manufacture Moderna’s Vaccine (mRNA-1273) Against Novel Coronavirus. Available online: https://investors.modernatx.com/news-releases/news-release-details/moderna-and-lonza-announce-worldwide-strategic-collaboration/ (accessed on 18 April 2021).

65. Wileman, H.; Mishra, A. Drug lag and key regulatory barriers in the emerging markets. Perspect. Clin. Res. 2010, 1, 51. [PubMed]

66. US Food & Drug Administration. Innovation to Respond to COVID-19. Available online: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-emergency-respond-covid-19 (accessed on 23 March 2021).

67. European Medicines Agency. EMA’s Governance during COVID-19 Pandemic. Available online: https://www.ema.europa.eu/en/news/ema-governance-during-covid-19-pandemic (accessed on 5 March 2021).

68. European Medicines Agency. EMA Establishes Task Force to Take Quick and Coordinated Regulatory Action Related to COVID-19 Medicines. Available online: https://www.ema.europa.eu/en/news/ema-establishes-task-force-take-quick-coordinated-regulatory-action-related-covid-19-medicines (accessed on 25 March 2021).

69. Critical Path Institute. Cure Drug Repurposing Collaboratory. Available online: https://c-path.org/programs/cdrc/ (accessed on 23 March 2021).

70. PwC. Pharma 2020: Supplying the Future-Which Path Will You Take? Available online: https://www.pwc.com/gx/en/pharma-life-sciences/pharma-2020/assets/pharma-2020-supplying-the-future.pdf (accessed on 19 April 2021).

71. Thomson, K.; Nachlis, H. Emergency use authorizations during the COVID-19 pandemic: Lessons from hydroxychloroquine for vaccine authorization and approval. JAMA 2020, 324, 1282–1283. [CrossRef] [PubMed]

72. US Food & Drug Administration. Letter of Authorization-Chloroquine Phosphate and Hydroxychloroquine Sulfate. Available online: https://www.fda.gov/media/136534/download (accessed on 4 March 2021).

73. US Food & Drug Administration. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. Available online: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and (accessed on 4 March 2021).

74. Nachlis, H. The FDA’s Evolving COVID-19 Emergency Use Authorizations: How The Convalescent Plasma Authorization Can Inform Future Vaccine And Therapeutic EUAs. Available online: https://www.healthaffairs.org/do/10.1377/hblog20201016.659416/full/ (accessed on 8 April 2021).