CHALLENGES AND OPPORTUNITIES OF DRUG REPURPOSING: A COST-EFFECTIVE STRATEGY FOR PRODUCT DEVELOPMENT AND NEW MARKET DEMAND

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ABSTRACT

The drug repurposing is essentially a re-positioning of the drug for a different disease or medical condition from already created and licensed to treat another set of indications/ symptoms of the original disease or medical condition. The various existing antiviral previously developed for the treatment of severe acute respiratory syndrome, malaria, HIV/AIDS has been identified as possible therapies for COVID-19. The main objectives of the study are to (a) explore the market demand of re-purposed drugs during COVID-19; (b) Analyzing the conventional drug production method to drug repurposing, evaluate the possible cost savings; (c) understand the emergency approval process during Covid-19; (d) explore how the pharmaceutical companies develop their new market with the repurposed drugs and (e) explore how the repurposing of drugs play a key role in the prolonged product life cycle of a drug. A descriptive study was performed. As of date the total volume of sales by different pharmaceutical firms and the corresponding total market value of the drugs used in COVID-19 including Remdesivir and other drugs stand at approximately Rs 2000-2500 crores. Of the 28 drugs approved by the USFDA (including both novel and repurposed) in the first quarter of 2020, 12 drugs were repurposed. The product development of repurposed drugs can be more rapid and cost-effective than the traditional discovery and development of drugs. The pharmaceutical companies have been active in developing their new markets with fresh target customers/ physicians where they can use the original brand equity with different indications to sell it.

Keywords	repurposed drugs, market development, product development, product life cycle, cost-effectiveness
JEL Classification	I11, I15, M31
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INTRODUCTION

Drug repurposing (DR) is also known as drug redirection, drug recycling, drug reprofiling, and therapeutic shift. It is a method of discriminating between FDA-approved/pro-drugs/failed/old/investigational/already marketed/existing for new pharmacological indications (Rudrapal M. et al., 2020). Outbreaks of emerging new infections such as coronavirus disease 2019 (COVID-19) have specific challenges for health practitioners to select suitable therapeutic/pharmacological therapies in the clinical setting with very little time available to develop new drugs. It is cost-effective to study the current antiviral and other drugs against SARS-CoV2 because of the time and cost needed to develop new therapies (Singh T.U. et al., 2020). The reuse of widely prescribed medications to avoid SARS-CoV-2 infection or COVID-19-associated respiratory symptoms can accelerate the development of a viable therapeutic alternative and quickly boost the current global crisis. Over 360 ongoing clinical trials are testing the effectiveness of various compounds against COVID-19(Duarte R.R et al., 2020). The Food and Drug Administration (FDA) of the United States continues to play a key role in the government's multifaceted response to the COVID-19 pandemic. It involves promoting medical countermeasures for the treatment and prevention of the epidemic, tracking possible shortages or disturbances of medical goods and food supply chains, and helping to minimize such impacts as necessary (FDA news release., 2020). Recently, the repurposing of available drugs for the treatment of many disease conditions has become increasingly common; it uses de-risked compounds with recognized preclinical, pharmacokinetic, pharmacodynamic profiles that can reach phase III or IV clinical trials directly, making the drug development process potentially low-cost and relatively rapid. Therefore, the World Health Organization (WHO) and other health organizations have opted to solve emerging health issues by reassessing the effectiveness of approved and experimental drugs (Singh T.U et al., 2020). WHO has identified several treatments that are most promising and approved for emergency usages, such as a combination of two HIV drugs (lopinavir and ritonavir), anti-malarial drugs (chloroquine and hydroxychloroquine), and an experimental antiviral compound Remdesivir. It was necessary due to the absence of effective medications against SARS-CoV2 as well as public health emergencies (Singh T.U et al., 2020).

OBJECTIVES

The main objectives of the study are:

1. To explore the market demand of re-purposed drugs during COVID-19;
2. To analyze the conventional drug production method to drug repurposing and evaluate the possible cost savings;
3. To understand the emergency approval process during COVID -19;
4. To explore how the pharmaceutical companies develop their new market with the repurposed drugs
5. To explore how the repurposing of drugs plays a key role in a drug's prolonged product life cycle.

LITERATURE REVIEW

At present, there are no prophylactic or preventive treatment options for COVID-19 approved by the Food and Drug Administration (FDA). This puts immense pressure on the FDA to rapidly create new therapies (Cassidy Christine et al., 2020). The typical drug production method takes place in stages: discovery and growth, preclinical testing, clinical trials; the FDA will perform a review and post-marketing monitoring. (Sullivan, T., 2020). One of the best ways to find safe and efficient treatment choices is by repurposing an already FDA-approved therapeutic. In the battle against COVID-19, therapeutic repurposing has been used (Gao J et al., 2020).

METHODOLOGY

The data is compiled from secondary sources, including published research articles, review articles, research indices like Google Scholar, Pubmed, and Wikipedia. The other data sources were from the US FDA official website, CSIR India, British Pharmacological Society, WIPO, News press releases, and surveys conducted from various market research agencies. A descriptive study is performed.

ANALYSIS AND DISCUSSION

A) Market Demand of Repurposed Drugs during COVID-19

CSIR listed the top 25 drug/drug candidates that can be effective in the treatment of COVID-19. This is an elaborate list, where many ongoing clinical trials are likely to affect the outcome results in changing the global therapeutic environment. There is a significant potential for many drugs to be licensed, which are not commercially available in India. The Council of Scientific Industrial Research (CSIR) has prioritized those drugs for developing through optimal synthetic processes. Developing the synthetic method for these top drug/drug candidates would increase the probability of an industry introducing drugs in India until favorable results are achieved in the outcomes of clinical trials. In addition to the top 25 medications mentioned above, other FDA-approved medications for repurposing for COVID-19 are being explored by CSIR labs (CSIR., 2020).

The epidemic began in Wuhan, China, and has spread worldwide, infecting nearly 109 million people with more than 2.41 Million cumulative deaths by February 14, 2021, according to WHO's global case dashboard COVID-19. In collaboration with some pharmaceutical companies such as Mylan, LAXAI, etc., CSIR has prioritized many other repurposed drugs that target the virus or the host pathways and is conducting many of these trials (CSIR., 2020).

On January 30, 2020, World Health Organization (WHO) declared COVID-19 as PHEIC (Public Health Emergency of International Concern) and pandemic on March 11, 2020 (NIH: National Institute of Allergy and Infectious Diseases., 2020). There is also an urgent need to tackle this highly infectious disease, which needs a thorough understanding of the disease's pathology and essential techniques for new drug detection. The other alternative treatments, such as the antiviral activity of natural killer cells and mesenchymal stem cells, immunotherapy, and Chinese traditional medicine, may be studied in addition to currently approved antiviral therapies. Many new therapeutic methods are emerging in these desperate situations, and more clinical trials are needed to ensure the safety and effectiveness of the new drugs (Parvathaneni. V et al., 2020). As the traditional method of the drug, production is tedious and costly, the repurposing of existing COVID-19 drug molecules has become an elegant technique for the rapid development of successful therapies, as evident from wide-ranging knowledge on the effectiveness of antimalarial drugs, chloroquine, and hydroxychloroquine(Senanayake S.L. et al., 2020; Fan H.-H.et al.,2020; Chary M.A. et al.,2020). The most important benefit of repurposing drugs for COVID-19 treatments is the speed of availability for patients. The hospitals are overwhelmed with patients who have contracted the virus, for which there are no reliable therapies. The shortened timeline for development associated with repurposing the drugs could significantly speed up healthcare delivery to affected patients (Phelps.K. et al., 2020).

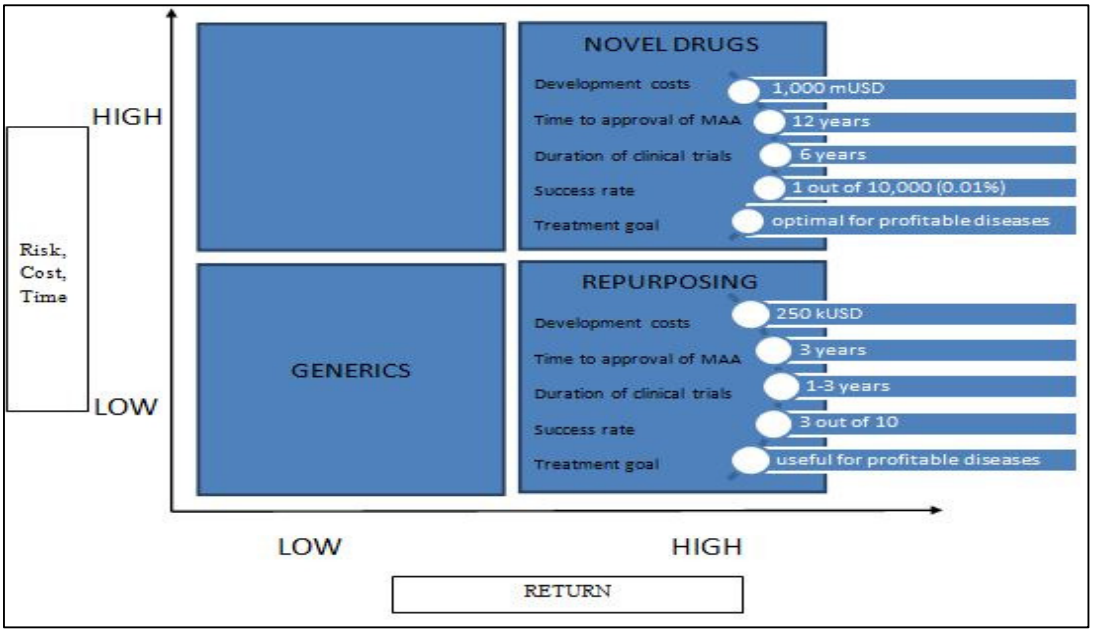
The repurposing and repositioning of medications provide market benefits. The worldwide medication repurposing market was worth almost $24.4 billion in 2015 and is projected to hit $31.3 billion by 2020, mirroring a 5.1 percent build yearly development rate (CAGR) over the course of the following five years. The United States dominated the business; it created $13.7 billion out of 2015 and is projected to reach almost $17.9 billion by 2020, mirroring a 5.4 percent CAGR throughout the following five years. With a CAGR of 4.7 percent, the non-US market is expected to grow to almost $13.4 billion by 2020, up from $ 10.6 billion out of 2015 (Arnum. P.V., 2016).

B) Analyzing the conventional drug production method to drug repurposing, evaluate the possible cost savings.

Both in terms of the financial investment necessary and the time is taken in expediting a drug in production to approval. The drug development process can be extremely expensive. The companies face a long period of drug development and clinical phase trials including, initial testing, drug synthesis, toxicity and effectiveness, API preparation, and formulation trials, before the clinical trial process for setting a path for creating a new drug. The early stages of the process of drug production can also be the most financially expensive, with firms committing hundreds of millions of dollars to a drug without ensuring it will make it to the market. Many upcoming pharmaceutical firms are working to repurpose or reposition existing drugs to shorten the road to production to cut down the drug development period and exploit

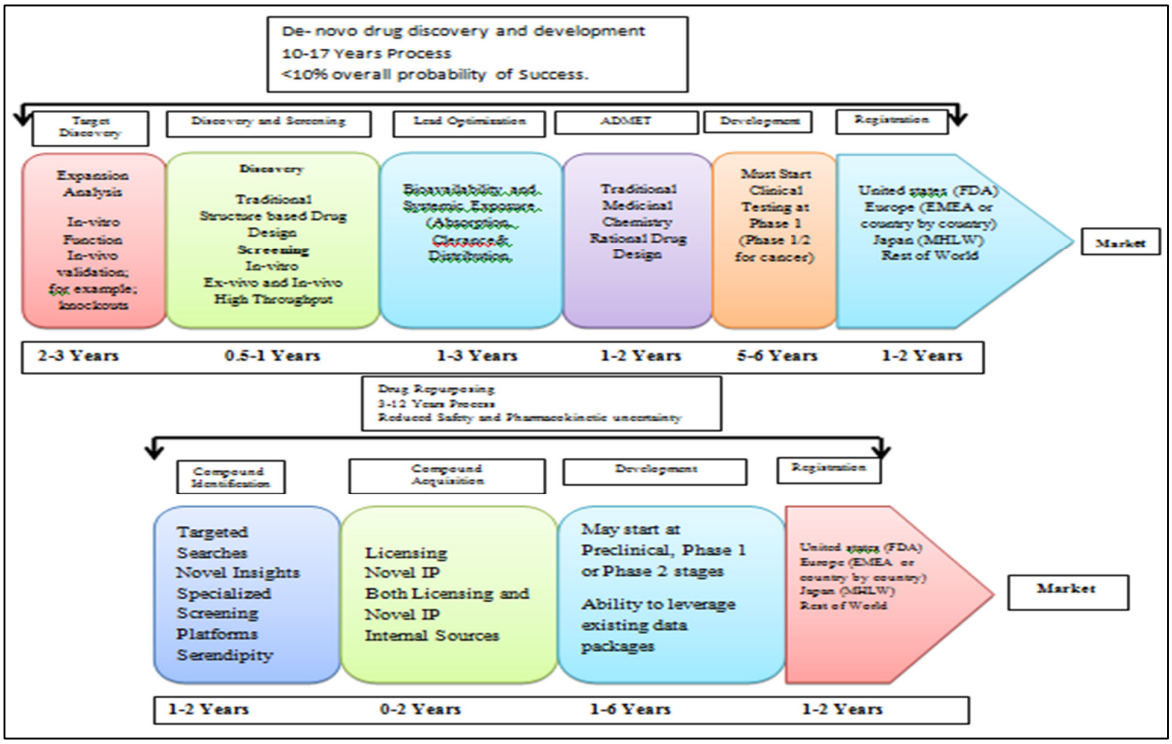
past companies' research and development work (Vanstone.K. et al.,2020). Therefore, drug repurposing with shorter timelines for production and streamlined studies contributes to substantial cost savings for the sponsor. With so many unanswered questions about effectiveness, moving quickly to the clinic carries tremendous risk, and the scale of production required for therapies with COVID-19 is enormous. Having a cost-optimized strategy for a well-understood active ingredient may allow a program to progress to approval or authorization, especially in uncertain funding and setting (Phelps.K. et al., 2020). Drug development and the transformation of scientific discoveries into new treatments enable biopharmaceutical companies to make considerable investments and resources. Many analyses in clinical fields show that it takes about 12 years and sometimes even longer to produce a new drug, from target selection to marketing authorization (Firgens.M. et al.,2020). The number of new drugs produced per billion dollars invested in R&D has experienced an exponential decrease over the past six decades. Consequentially, the total cost of selling a drug has risen from a few hundred million dollars in the 1990s to more than two billion dollars today. Today, less than a dollar of value is returned for each dollar invested by the pharmaceutical industry on R&D, indicating that potential R&D spending by businesses will decrease (National Academies Press (US)., 2020). The high failure rate of drug candidates in all phases of development is one cause of the declining return on investment. A clear response would be to "fail earlier" drugs in the development process to minimize the time and resources spent determining that a drug will not be successful; nevertheless, behavioral disincentives often interfere (e.g., market forces, job security, optimism about data on drug development) (National Academies Press (US)., 2020).

Figure 1: Comparison between traditional development methods (i.e., for new drugs and generics) and the strategy of repurposing development (Firgens.M. et al.,2020)



Source: Adapted from Firgens Michael 2018: Drug Repurposing – A Smart Development Strategy to Make Drug Development Cheaper, Faster, Safer And More Successful, 25th December 2020

Figure 2: Comparison of the method of drug development for (a) new and (b) repurposed drugs (Ashburn 2004)



Source: Adapted from Ashburn. T.T, & Thor, K. B. 2004: Drug repositioning: identifying and developing new uses for existing drugs. Nature Reviews Drug Discovery, 3(8), 673–683, 18th January 2021

C) Emergency Approval process during COVID-19

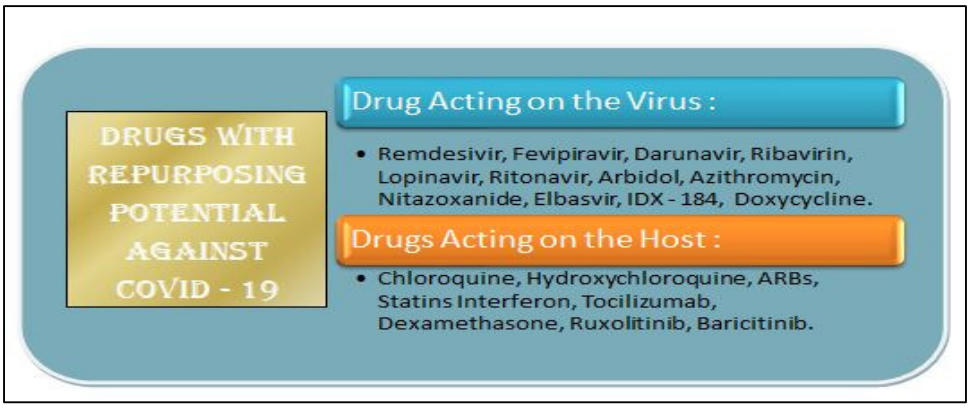
Under Federal Food, Drug, and Cosmetic Act, EUA(Emergency Use Authorization) was created for the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (USFDA., 2020). The FDA will give a EUA for "an unapproved Medication or an unapproved utilization of an affirmed clinical product" if the Secretary of Health and Human Services pronounces an emergency (Stroud et al., 2010). In a crisis, the EUA permits the FDA to permit the utilization of an investigational drug that shows guarantee, but needs adequate clinical preliminary proof for FDA endorsement due to time limitations (Cassidy et al.,2020). The FDA has historically given EUAs during previous epidemics/pandemics, such as Zika virus (2016), Enterovirus D68 (2015), Ebola virus (2014), Coronavirus (2013), H7N9 Influenza (2013), and, for the latest COVID-19 pandemic. The scientists have used existing SARS-CoV-2 replication data and cellular entry pathways to develop therapeutics and medications for COVID-19. One of the best ways to find safe and efficient treatment choices is by repurposing an already FDA-approved therapeutic. In the battle against COVID-19, therapeutic repurposing has been used (Gao.J. et al.,2020). The use of investigational drugs that have demonstrated preclinical effectiveness and protection for related illnesses is another path to drug production. The Remdesivir is a transitional medicine that has shown promise for the treatment of a disease (Amirian ES.,2020).

D) Pharmaceutical companies develop their new market with the repurposed drugs and how the repurposing of drugs play a key role in the prolonged product life cycle of a drug.

At any point in a product's discovery, growth, and life-cycle management, and the method of choosing a disease indication should be evaluated. Even if an initial indication of the disease is selected, there may be relatively little information about the mechanism or target. There could be several chances to re-evaluate indications during drug production. Besides, safety issues in more severe conditions, when adequate care is not available, lead to negative outcomes in patients. The value of financial rewards for corporations is that the number of patients compounded by the price of medication must exceed a certain minimum amount for a corporation to invest in the drug to make financial sense (although companies may provide drugs for philanthropic reasons). The company must also take into consideration how long the drug will be under patent protection. If a drug patent has expired or is close to expiring, the total profits available from that drug would be significantly smaller than for a drug with a significant patent life. The federal government promotes drug production for orphan diseases, but some diseases are still more likely to draw interest than others. Naturally, an illness affecting 199,000 patients is a more attractive target for the pharmaceutical companies than an illness of only 100 patients. While government incentives matter to businesses, they do not make an unattractive business opportunity sufficiently enticing to pursue. It is also time-consuming and expensive to move technology, and biotechnology company partners may lack sufficient financial resources to invest in the compound to see its production through effectively. There is a belief that the chances are slim that any given drug would result in a viable product line(National Academies Press (US); 2014).

Examples of Repurposed Drugs for the treatment against COVID-19

Figure 3: A list of drugs that could be repurposed for COVID-19. The drugs being considered for COVID primary therapy to operate on either the virus's or the host's targets.(Thakur. U.S. et al., 2020)



Source: Adapted from Singh Thakur Uttam, Parida Subhashree, Lingaraju Madhu Cholenahalli, KesavanManickam, Kumar Dinesh, Singh Raj Kumar 2020: Drug repurposing approach to fight COVID-19, January 8, 2021

Remdesivir: Remdesivir illustrates a transitional treatment recently tried as an anti- viral; however, it is not yet endorsed by the FDA. The drug showed prophylactic and therapeutic efficacy against MERS and SARS Coronaviruses in Rhesus macaques, indicating its potential against various coronaviruses such as SARS-CoV2. In a study performed at 13 sub sites and 60 sites in various parts of the world, the mortality rate was 11.9% with placebo (521 in the group) and 7.1% with Remdesivir (538 in the group) at 14 days in a total of 1,059 patients, respectively(Beigel J.H. et al.,2020). Another research, however, indicates differently that Remdesivir may not have such statistically significant clinical benefits while speaking in terms of count, patients are given Remdesivir showed a faster clinical improvement. Another clinical trial of Remdesivir in extreme COVID-19 patients without mechanical ventilation support showed no substantial difference between the 5-day and 10-day course of Remdesivir therapy (Goldman. J.D. et al., 2020).

Chloroquine and Hydroxychloroquine: Chloroquine, known mostly for its anti-plasmodium activities, also has antiviral efficacy. Originally derived from the Cinchona plant, this drug is now mainly a synthetic drug discovered by Bayer Laboratories (4-amino quinoline). The active inhibitors of most coronaviruses are chloroquine and its analogues (Devaux C.A. et.al., 2020). It is hypothesized that to prevent SARS-CoV2 infection, hydroxychloroquine could achieve concentration in the above tissues with a safe dose. The WHO recently stopped the Solidarity Study arm of hydroxychloroquine from finding an appropriate cure for COVID-19. These findings found that hydroxychloroquine did not contribute to a decrease in the mortality of COVID-19 hospitalized patients relative to standard treatment (briefed on 17 June 2020 by WHO; Thakur. U.S. et al., 2020; Yusuf. I.H. et al., 2017). Besides, the use of chloroquine and hydroxychloroquine may be required both in the prophylaxis technique and in patients with a higher number of clinical trials with COVID-19. Hydroxychloroquine was the first pandemic drug released by the FDA to the EUA. The EUA offered access to potentially promising medication for COVID-19 patients in the absence of any FDA-approved treatment options. Therefore, EUA made hydroxychloroquine widely available to COVID-19 patients, which in turn made it possible to obtain substantial data, perform clinical studies and interpret data on hydroxychloroquine in COVID-19 humans. This helped doctors, scientists, and the FDA draw early conclusions regarding successful vs. unsuccessful COVID-19 therapies. (Cassidy.C. et al., 2020).

Dexamethasone: Dexamethasone is a corticosteroid, and several clinical trials have used it. However, few questions have arisen about the outcome of the recovery trial in selecting the dosage and the right steroid. Furthermore, in the recovery study, the effect of dexamethasone in geriatric patients and the effects on viral load are not reported. (Johnson R.M. et al., 2020). Using this drug can lead to decreased viral clearance and nosocomial (secondary) infections in the recovery process. It can suppress immunity and aggravate such latent infections, the frequency of which is of little concern to developed countries. Therefore, before implementing COVID-19 therapy, region-specific study is required (Brotherton.H. et.al., 2020; Theoharides .T.C. et.al., 2020;Thakur .U.S. et.al., 2020).

Azithromycin: Azithromycin, a broad-spectrum antibiotic that has anti-inflammatory effects, has been tested in fewer trials. Azithromycin is widely used for bacterial respiratory infections and can potentially treat or prevent SARS-CoV-2 co-infection. Azithromycin may have antiviral activity against some RNA viruses as well. In addition to SARS-CoV-2, azithromycin is

in vitro effective against viruses such as Zika and rhinovirus; it also has antiviral effects on bronchial epithelial cells. Azithromycin is readily available and has an outstanding safety profile, so it could be easily scaled up as a first-line treatment for patients with COVID-19 if shown to be successful. The results of trials suggest that azithromycin might not provide benefit to patients once the disease has progressed and patients require hospitalization. Since azithromycin is currently the most commonly prescribed outpatient therapy for COVID-19, establishing whether azithromycin is helpful earlier in the disease course is an important research priority. If azithromycin does not play a role in COVID-19 therapy, avoiding its use will minimize the excessive intake of antibiotics (Oldenburg . C.E et al., 2020).

CONCLUSION

COVID-19 is a pandemic, which has no cure to date, including vaccines and medications. However, there is a range of FDA-approved medications available to treat other diseases that may be used based on the COVID-19 trial and are called repurposed drugs. Instead of the expensive and time-consuming traditional drug discovery route, which has a higher failure rate, drug repurposing is becoming a promising option for drug production. Drug repurposing allows the discovery in shorter timeframes for new applications of old medications; it is thus becoming cost-effective, thereby eventually benefiting patients and the overall healthcare system. In the future, to conclude its use in COVID-19 patients, chloroquine and hydroxychloroquine require a significant number of clinical trials. Some medications are in the premature stages of investigation to be used against COVID-19, such as ivermectin, and these agents may be potential therapeutic agents in the future. A highly effective way of exploiting drugs with proven safety profiles to tackle the coronavirus outbreak is to repurpose FDA-approved drugs. However, a proper delivery system and delivery route must be selected to reduce and deliver repurposed drugs locally to the target site. Repurposing may be a great possibility with clinical delivery intervention. To treat infections caused by various viruses such as SARS-CoV-2, it is important to focus rapidly on collaborative drug repurposing research and optimal drug delivery strategies and inhaler devices.

From drug development to manufacturing to legislation to consumer access and health care, the COVID-19 pandemic has taught us that the entire healthcare ecosystem must become more successful and beneficial to patients.

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