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Drug Approval During the Covid-19 Pandemic: Following the Evidence

Testimony of:

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Summary of Major Points

- Repurposing existing therapeutic agents allows opportunities for expedited clinical trials, and if found safe and effective, repurposed medications can be inexpensive and widely available options to treat patients with Covid-19.
- The pandemic has made it possible for high-quality clinical trials of potential therapies to be performed swiftly, due to a large volume of available patients to enroll and short disease course that allows for speedy measurement of important clinical outcomes.
- Observational studies based on real-world data can be a powerful, efficient tool to provide preliminary or additional evidence complementing clinical trials, but these studies must be high quality and methodologically rigorous.
- Most of the important evidence about which repurposed drugs are effective in Covid-19 has been publicly funded, and government funding is particularly important for repurposed drugs for which financial incentives for industry may be limited.
- Even before approving drugs, during a public health emergency the FDA has broad authority to authorize use of medications based on preliminary evidence.
- **Learning from our experience so far, Congress should take four actions to improve the process for studying and approving repurposed drugs moving forward.**
    1. Hold all government agencies and officials accountable to make statements and act based on the highest-quality available evidence; patients and providers rely on this information to guide evidence-based clinical practice.
    2. Further invest in research, either directly or through collaboration with academic institutions, and assure that drugs which receive federal funding will be priced fairly and made available equitably.
    3. Establish a centralized public health infrastructure and clinical trial network that can allow the federal government to take the lead on setting the research agenda, streamlining trials across multiple sites, reducing duplicative efforts, and improving the speed at which clinical trials can be performed.
    4. Make several improvements to the FDA's Emergency Use Authorization (EUA) process, including:
        - Clarifying and standardizing the level of evidence required to support an EUA, including the potential role of high-quality observational studies.
        - Increasing transparency by requiring all data informing the EUA be made publicly available at the time it is issued.
        - Outlining a robust plan for fair and equitable distribution of the product subject to the EUA and for negotiation with the product's manufacturer for a fair price.
        - Requiring ongoing collection of patient outcome data to support a product's safety and effectiveness while the EUA is in effect and the product has not yet been approved by the FDA.

Chairman Foster, Ranking Member Norman, and Members of the Investigations and Oversight Subcommittee:

My name is Benjamin Rome. I am a practicing primary care physician and a health policy researcher at Harvard Medical School and in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital in Boston. Within the Division, I am a member of the Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research group that studies the intersections between prescription drug affordability and use, laws and regulations related to medications, and the development and cost of drugs. I am honored to be here today to talk with you about the process of studying and approving drugs during the Covid-19 pandemic, with a focus on the best way to evaluate existing medications that might be repurposed to treat patients during this public health emergency.

Drug Approval During Covid-19

The global Covid-19 pandemic has kicked of an urgent search for effective therapies and has put pressure on the US Food and Drug Administration (FDA) to swiftly make medications available to patients. The need to act expeditiously has also encouraged us to consider whether existing medications that we already have experience using for different indications might be repurposed and tested for effectiveness in treating Covid-19. Even remdesivir – an experimental antiviral drug that was recently shown to be effective in Covid-19[1] – was initially developed to treat hepatitis C and was subsequently tested unsuccessfully in patients with Ebola before being repurposed during the current pandemic.[2] Drug development can be a lengthy process, in which human clinical trials are only the final step. Thus, the decision to repurpose several drugs that have existing data in humans allowed clinical trials to begin early in the pandemic. Even prior to Covid-19, repurposing drugs for new indications was common. Among 26 transformative drug products or drug classes approved by the FDA from 1984-2009, our group found that 35% were repurposed after being initially studied for a different indication.[3]

In many ways, the search for Covid-19 therapies can already be considered a success. Just 4 months after the first patient with Covid-19 was reported in the US, two repurposed drugs have now demonstrated efficacy for treatment of Covid-19 and are available for use by US patients: remdesivir and dexamethasone.[1,4] Remdesivir use is now allowed under an FDA

Emergency Use Authorization (EUA), and dexamethasone is a low-cost generic corticosteroid that can readily be prescribed by clinicians.

However, our nation's response to Covid-19 has also shown examples of how the process for testing and approving drugs can go awry, as illustrated in the case of hydroxychloroquine.[5] Early studies showed that the hydroxychloroquine had in-vitro activity against the virus that causes Covid-19,[6] spurring interest in potentially repurposing the drug for use in Covid-19. In mid-March 2020, a small study of 36 patients in France reported that those who received hydroxychloroquine, particularly in combination with the antibiotic azithromycin, had faster clearance of the virus based on nasopharyngeal samples, compared to untreated controls.[7] The study was subsequently criticized for obvious methodologic flaws, including baseline differences between the treated and control patients, substantial amounts of missing data, and exclusion of patients who did not complete the study due to side effects or death.[8]

However, shortly after this study was published, President Donald Trump stated that hydroxychloroquine and azithromycin could be "one of the biggest game changers in the history of medicine."[9] He continued to advocate heavily for use of the drug and even claimed to have taken it himself to prevent Covid-19[10] despite no evidence that the drug was effective for that purpose. On March 28, the FDA issued an Emergency Use Authorization (EUA) for hydroxychloroquine and the related drug chloroquine for use among patients with Covid-19. The scope of the EUA was limited to permitting distribution of 30 million doses that were donated by the drug's manufacturer to the US Strategic National Stockpile.[11,12] However, the EUA was widely yet incorrectly reported by President Trump and others to mean that the FDA had approved the drugs for Covid-19.

Because hydroxychloroquine was already approved for use in patients with rheumatoid arthritis and lupus, it was easily available for clinicians to prescribe it "off label" to treat or prevent Covid-19, and demand for the drug spiked immediately after President Trump's initial endorsement.[13] This led to widespread shortages at pharmacies, which resulted in difficulty obtaining the medication among patients with rheumatoid arthritis and lupus, two conditions in which hydroxychloroquine has been shown to have benefits that outweigh its risks.[14] By contrast, there were concerns raised about the drug's known cardiac toxicities, particularly because there was not yet any convincing evidence of benefit when using the drug to treat Covid-

19, as well as concerns about accidental poisonings among patients who confused the drug with non-medical chloroquine-containing products.[13] In response to these concerns, on April 24 the FDA issued a warning cautioning against the use of hydroxychloroquine to treat Covid-19 outside of a hospital or clinical trial setting,[15] though the EUA remained in effect.

Ultimately, more evidence about the risks and benefits of hydroxychloroquine in patients with Covid-19 emerged. Two larger observational studies of several thousand patients in New York found no association between use of hydroxychloroquine and improved clinical outcomes.[16,17] In early June 2020, results were reported from two large randomized controlled trials finding that hydroxychloroquine was not effective either for preventing Covid-19 symptoms after exposure to the virus or for treatment of hospitalized patients with confirmed Covid-19.[18,19] Ultimately, the FDA withdrew the EUA for hydroxychloroquine on June 15.[20]

Maintaining Rigorous Standards for Evidence

The case of hydroxychloroquine highlights the importance of focusing attention and resources on rigorous, high-quality evidence to determine whether potential treatments are safe and effective. All drugs marketed in the US must be deemed to have "substantial evidence" of safety and effectiveness by the FDA.[21] While the FDA traditionally preferred two high-quality randomized controlled trials in which a drug is compared to placebo and patients and investigators are blinded to treatment assignment, this standard has been eroded over the past few decades. More recently, the FDA frequently determines that drugs meet the "substantial evidence" standard based on more limited evidence, especially if the drug treats a disease that is life-threatening or rare or when there is an unmet medical need.[21] Over the past several decades, the FDA has approved an increasing proportion of drugs through expedited approval pathways, with 81% of newly-approved drugs benefiting from at least one such pathway in 2018.[22] As a result, many drugs are now deemed safe and effective by the FDA based on a single clinical trial, trials with suboptimal design (e.g., lacking randomization or blinding), or trials that rely on surrogate outcome measures (such as changes to lab tests or radiology findings) which may or may not predict actual clinical benefit for patients.[22]

While it is tempting to believe that the FDA should rely on limited evidence given the urgent need for effective Covid-19 therapies, it would be a mistake to abandon the process of

carefully evaluating medications that has served us so well for many decades. In fact, the pandemic presents several conditions needed to expeditiously obtain rigorous clinical trial evidence. First, the entire global scientific community is united around finding treatments for Covid-19, with increased resources directed toward streamlining the regulatory and ethical review processes to prevent delays. The first randomized controlled trial began enrolling patients in China just one week after the virus had been identified.[23,24] As of May 11, 2020, there were 144 active clinical trials of therapeutic agents to treat Covid-19,[25] including several international trials testing multiple potential therapies at once.[4,26]

Second, the thousands of patients presenting each day to emergencies rooms and hospitals for treatment of Covid-19 allows for rapid enrollment into clinical trials, and patients have been very willing to participate. In the key clinical trial of remdesivir, 96% of the 1,107 patients assessed for eligibility were enrolled and randomized, an impressive feat for a trial of an experimental therapy versus placebo.[1] Third, because Covid-19 is an infectious disease with rapid progression or recovery, important clinical outcomes such as death, hospitalization, and need for a ventilator, can be quickly measured and used to judge the effectiveness of treatments.

Finally, once effective therapies are identified, FDA can expedite its regulatory review and quickly get the medication into the hands of doctors and patients. The FDA created a Coronavirus Treatment Acceleration Program to assist manufacturers in navigating regulatory requirements to and assure an expedited review process for any Covid-19 therapies that did prove effective.[25]

Thus, several aspects of the pandemic make it more feasible than ever to expeditiously conduct high-quality, rigorous randomized clinical trials that provide the best possible evidence of whether therapies are safe and effective. So far, this process has identified two drugs that either shorten duration of symptoms or reduce the risk of death in patients with Covid-19 – remdesivir and dexamethasone.[1,4] Trials of other drugs, including hydroxychloroquine and the antiviral combination lopinavir-ritonavir, have provided useful evidence that those drugs are *not* effective.[18,19,23]

Because many repurposed treatments are being used for routine care even prior to clinical trial results, researchers have attempted to use observational ("real world") data to provide early evidence about whether treatments are associated with improved outcomes. Large observational

studies, which use real-world patient data either from insurance claims or electronic health records, can provide early data when clinical studies are not feasible or have not yet been completed, and can offer complementary information to what is learned from clinical trials.[27–29] For example, clinical trials often do not include a sufficient number of patients to detect rare adverse effects, so observational data of thousands of patients can measure safety issues that were not noticed in the pre-approval clinical trials after drugs are approved by the FDA.[30] There is even evidence that observational data might be used confirm effectiveness of an existing mediation for a novel indication.[31]

However, observational research presents many potential methodologic challenges and must be performed well to assure validity of the results. For example, clinicians may reserve experimental Covid-19 therapies for the most severe cases, making it challenging to compare patients who received a drug to those who did not. Furthermore, certain key information may not be captured in available real-world databases. Nonetheless, research using these methods to study the safety and effectiveness of hydroxychloroquine and angiotensin-receptor blockers among Covid-19 patients has provided important preliminary evidence and informed clinical practice at the height of the pandemic.[16,17,32] While high-quality observational studies can provide useful evidence about use of repurposed drugs, the FDA should be not approve any new drug based on observational studies alone, without confirmatory evidence for clinical trials. Additionally, observational studies must be meticulously performed and rigorously vetted to assure that the data used is of high fidelity. Recently, both the *New England Journal of Medicine* and *The Lancet* issued retractions after concerns were raised about the provenance of a large international dataset used in these studies.[33,34] These retractions further underscore the importance of rigorous conduct and methodologic review of observational studies to assure that the results are reproducible and valid.

Opportunities for Federal Investment

While pharmaceutical companies are typically involved in development of new drugs, investment in research by the federal government also plays an important role. Federally funded basic and translational science were found to be related to every single new drug approved from

2010-2016. In addition, our group recently reported that publicly-supported research played a major role in the late-stage development 1 in 4 drugs approved over the last decade.[35]

Federal funding of research has played a critical role during the Covid-19 pandemic, and additional investment could expedite clinical studies necessary to learn whether drugs are safe and effective. This is particularly true for repurposed drugs, many of which are older and inexpensive, providing limited incentives for the for-profit brand-name pharmaceutical industry to study these drugs in Covid-19 patients. Indeed, the RECOVERY trial, which has already produced useful results for both hydroxychloroquine and dexamethasone, was funded by the United Kingdom's National Institute for Health Research.[4] But even when a drug is patent-protected, public investment has played an important role. While the intellectual property for remdesivir is owned by Gilead Sciences, the key clinical trial that has supported its use in Covid-19 was funded by the US federal government.[1]

By investing in clinical trials, the federal government can help expedite and prioritize the development of high-quality evidence to guide our use of therapeutics for Covid-19, particularly in the case of repurposed drugs. Furthermore, efforts in Europe have shown that a coordinated effort nationally across the health care system can result in expedited clinical trial results. Thus, by investing in a robust public health infrastructure and clinical trial network, the federal government could improve the US role in establishing a research agenda, facilitate collaborative research across multiple sites, and streamline efficiency by cutting down on duplicative efforts.

Improving Use of Medications Prior to FDA Approval

Naturally, during the pandemic there has been public demand to allow use of medications even before the FDA has had a chance to weigh the risks and benefits. There are several ways patients can access unapproved medications, with implications for the practice of evidence-based medicine.

First, medications that are already approved by the FDA and marketed for a different indication can be used "off-label" by physicians to treat Covid-19. While the FDA approves drugs for only those indications on which there is evidence of safety and effectiveness, clinicians can use the drugs for any indication within the realm of the practice of medicine. As a result, medications like hydroxychloroquine have been widely prescribed to patients even before

evidence had been collected about their safety and effectiveness. However, there is no rigorous tracking of clinical outcomes among patients prescribed drugs off-label, which limits our ability to use these experiences to learn about drugs' safety and effectiveness to guide evidence-based clinical decision-making.

Additionally, for investigational drugs that are not yet marketed, patients who are severely ill, lack alternative treatment options, and are not eligible for clinical trials may be eligible for "expanded access" programs.[36] The FDA nearly always grants permission for expanded access requests, and it is mainly up to manufacturers whether they will make their drug available to patients outside of clinical trials. This option was used for remdesivir, which Gilead provided to over a thousand Covid-19 patients outside of clinical trials.[37] Even before the Covid-19 pandemic, many conservative politicians and advocacy groups have supported expanding patients' "right to try" unapproved experimental medications.[38] This sentiment stems from an incorrect assumption that slow and onerous FDA requirements limit patient access to important and beneficial medications. To the contrary: the FDA approves the overwhelming majority of new drug applications it receives, with recent review times averaging less than one year and 6 months or less for truly innovative new treatments.[22] Currently, the FDA is one of the fastest and most efficient pharmaceutical regulatory agencies in the world, and a majority of drugs are approved in the US before being approved in Europe or Canada.[39]

Finally, during a public health emergency the FDA has broad regulatory authority to allow for use of unapproved drugs through Emergency Use Authorizations (EUAs). The FDA's authority to issue EUAs was first granted by Congress under the Project BioShield Act of 2004. While EUAs are typically used to allow rapid deployment and expansion of diagnostic testing and necessary devices (including personal protective equipment), the FDA can issue an EUA to allow use of a drug if it is "reasonable to believe" that the drug may be effective and the known and potential benefits outweigh the known and potential risks, based on "the totality of scientific evidence available."[40]

Prior to the Covid-19 pandemic, the only instance for which EUAs were used to permit use of medications for unapproved indications was during the 2009-2010 "swine flu" outbreak. At that time, an EUA was issued for use of peramivir – an investigational intravenous drug to treat influenza – in severely ill hospitalized patients with H1N1 influenza.[41] The EUA was based

on preliminary evidence from phase 2 and phase 3 clinical trials,[42] and the drug was given to approximately 1200-1500 patients, though there was no rigorous tracking of which patients received the drug or clinical outcome data.[43–45] Ultimately, a clinical trial showed that peramivir was not effective for treatment of severely ill hospitalized influenza patients, and the drug was approved by the FDA only for use in less sick, uncomplicated cases. Because the drug is administered intravenously and there are similar drugs from the same class that can be taken as pills (oseltamivir, also known as Tamiflu), the current use of peramivir is very limited.

During the current pandemic, the FDA has issued two EUAs for medications under two very different circumstances. The first, for hydroxychloroquine and chloroquine, was based on "limited in-vitro and anecdotal clinical data in case series," with no clear documentation of the specific evidence the FDA considered when making its decision.[42] Although the EUA was intended to increase access to the medications through use of the Strategic National Stockpile, the EUA instead signaled to providers that the drugs had been judged to be effective and—along with misleading statements by some politicians, celebrities, and media outlets—helped spur widespread off-label use that caused shortages of the drugs among patients who relied on them to treat rheumatoid arthritis and lupus.[14,42]

More recently, the FDA issued an EUA for use of remdesivir after preliminary clinical trial evidence found that the drug shortened duration of symptoms.[1] Because remdesivir is not yet approved or marketed in the US, the EUA provided a means for Gilead to begin distribution of the drug for use in US hospitals, which was kicked off by a donation of 1.5 million doses of the drug to the federal government. However, the process by which these doses of remdesivir was distributed was opaque, and it was not clear how the available supply of remdesivir was being equitably allocated to where it was most needed.[46] Furthermore, at the time the EUA was issued, the only publicly-available data to guide clinicians were top-line results from a press release; the full preliminary results were not published until 3 weeks later,[1] at which point distribution and use of remdesivir outside of clinical trial settings was already underway. Finally, because Gilead owns patents protecting remdesivir, they will be able to price the drug however they choose, and there has been no coordinated federal effort to negotiate a fair price based on the drug's value so that cost does not limit patient access.

Summary and Recommendations

The Covid-19 pandemic has highlighted both opportunities and challenges within the US drug approval process. Our use of repurposed medications has allowed rapid development and execution of several high-quality clinical trials, and we now have proof that such trials can feasibly be conducted in a short time frame. So far, trials have provided solid evidence relating to at least four potential drugs for Covid-19, of which two have proven effective. But along the way, there have been several missteps that we should learn from as we move forward and continue to study and develop therapies to treat and prevent Covid-19. Our experiences so far point toward four key actions Congress should take to improve the process by which existing drugs are repurposed and studied for use in Covid-19.

First, Congress should hold all government agencies and officials accountable for making statements and acting based on the best available scientific evidence. From the case of hydroxychloroquine, we have learned that promotion of a drug by politicians and explicit or implicit validation of a drug by government agencies based on limited evidence can have consequences. Scores of patients were exposed to the risks of hydroxychloroquine, which turned out not to be effective. Furthermore, the immense attention devoted to hydroxychloroquine over the past several months may have diminished resources that could have been dedicated to other potential therapies. The FDA's issuance of an EUA based on limited evidence and subsequent warnings about the drug safety sent mixed signals to patients and prescribers that caused confusion, hampered clinical trial enrollment, and may have diminished the public's trust. For its part, the scientific community must continue to scrutinize the quality and methodologic rigor of all published peer-reviewed research, as highlighted by recent retractions from two of the world's leading medical journals of studies that were based on flawed underlying data.

Second, Congress should invest heavily in the organization and conduct of high-quality clinical trials and observational studies, which we know can swiftly provide evidence for safety and effectiveness of therapies in Covid-19. Most of the highest quality evidence generated to date during the pandemic has resulted from public funding, including the US government in the case of remdesivir and the UK government in the case of dexamethasone. While industry will continue to play a role, the federal government's leadership and involvement are crucial, particularly for repurposed drugs for which industry may have little or no financial incentive to

conduct clinical studies. However, such public investment should be made with the assurance that any medications found effective will be priced fairly and distributed equitably to patients who need them. No American should be prevented from accessing a potentially lifesaving treatment for Covid-19 due to cost, especially when taxpayers fund the research supporting the drug's use.

Third, Congress should invest in in a public health infrastructure and national clinical trial network that allows for a coordinated response by shaping the research agenda, facilitating research across multiple sites, and limiting duplicative efforts. In several European countries, government and academics have collaborated on large, multi-site studies that test multiple repurposed drugs simultaneously. A prime example is the RECOVERY trial, which has already provided useful information about the lack of effectiveness of hydroxychloroquine and the effectiveness of dexamethasone. The Covid-19 pandemic is far from over, and investment in a similar infrastructure in the US can promote collaboration to expedite our ability to uncover additional therapies to treat or prevent Covid-19, including vaccines.

Finally, Congress should amend the process by which the FDA issues Emergency Use Authorizations (EUAs) to expand access to drugs before they are formally approved. The level of evidence and data required to meet the "reasonable to believe" standard should be made clearer, including the role of high-quality observational studies. While the EUA for hydroxychloroquine and chloroquine was based on "preclinical and limited anecdotal" evidence that turned out to be unreliable, the remdesivir EUA was not issued until there were clinical trial results. Any data the FDA uses should be described, and full results should be made publicly available at the time an EUA is issued. This was not the case for either EUA issued for drugs during the Covid-19 pandemic so far, and Congress could act to compel the FDA to increase transparency for all future EUAs. Additionally, as new evidence emerges, the FDA should be directed to apply the same standards for revoking an EUA as required for approving it; the hydroxychloroquine EUA lasted for 3 months despite multiple studies released during that time that raised questions about the drug's safety and effectiveness. Even while the EUA was in place, the FDA issued a warning cautioning against use of the drug due to serious cardiac risk. A more predictable set of rules around EUAs will promote public understanding, make it easier for physicians like me to know how to best treat patients, and enhance trust in government.

The issuance of an EUA should also be accompanied by a clear and transparent plan for how the drug will be fairly and equitably distributed to patients. It is not clear how the federal government allocated the doses of hydroxychloroquine or remdesivir that were provided by manufacturers or whether the EUAs satisfactorily improved access to either medication. Finally, issuance of an EUA should be accompanied by collection of demographic, treatment, and outcome information for all treated patients to gain additional insight about the drug's safety and effectiveness. A federal registry operated by the FDA or an independent third party could help find early safety signals not detected clinical trials, monitor for disparities in access to the drug, and expand upon effectiveness data from clinical trials. Failure to collect such information may hinder efforts to sufficiently understand a drug's safety and effectiveness to support FDA approval.

The Covid-19 pandemic has caused many to suggest that we must balance the desire for rapid use of experimental treatments against the need for rigorous evidence of drugs' safety and effectiveness. However, we have learned that we need not choose between rigorous scientific study and speed – we can have both. In a recent viewpoint published in *The New England Journal of Medicine,* Dr. Jerry Avorn and I argued that "The health of individual patients and the public at large will be best served by remaining true to our time-tested approach to clinical trial evidence and drug evaluation." As our fight to control the Covid-19 pandemic continues, Congress must assure that we uphold a drug approval process that follows the science and promotes evidence-based medical practice.

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