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"Repurposing Therapeutic Drugs for COVID-19; Research Challenges and Opportunities"

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I want to thank Chairman Foster, Ranking Member Norman, and other committee members for inviting me to be a witness on behalf of the Center for Science in the Public Interest (CSPI) at this important hearing. CSPI is an almost 50-year-old advocacy group that is a watchdog on food and health issues on behalf of US consumers. We have been actively involved in COVID-19 issues, including building an online hub that aggregates all international databases containing evidence on COVID-19 (https://cspinet.org/covid-19-evidence-hub) and advocating for better workplace protections, particularly for those in the meatpacking industry.

The COVID-19 epidemic has produced unparalleled amounts of scientific information and has done so more rapidly than ever in history, as thousands of researchers across the globe have turned their attention to the disease. By one estimate, perhaps 52,000 papers will have been completed by mid-June. One particular focus of research has been repurposing existing drugs to treat COVID-19. This approach has an understandable allure: Such a drug would already be produced on a large scale, the product would have been found effective by the Food and Drug Administration (FDA) or other regulatory authority for a particular use, the sponsor would have

submitted data regarding the safety of the drug, and physicians would have experience prescribing it.

Unfortunately, it's not so simple. Effectiveness for one condition does not guarantee effectiveness for a second condition, even a closely related one. The target populations may be demographically and medically different and so even the existing safety database and clinical experience may have only limited relevance. The product may need to be administered in different doses or by different routes than for the first condition. Together, these factors require that FDA conduct a unique risk-benefit assessment for the potential new use.

Sad to say, shortcuts do not come often in science. And our experience with two repurposed drugs in the COVID-19 pandemic reinforces the need to adhere to established scientific principles.

The experience with the anti-malarial drugs chloroquine and hydroxychloroquine (which I will consider as one drug for the purposes of this testimony) illustrates how data-free speculation can have disastrous consequences. The drug was frequently mentioned as a potential treatment for viral infections in the past, but, despite some promising early findings in laboratory testing, it never proved effective at preventing or treating those infections in clinical studies. It would likely have languished well down the list of candidate therapies for COVID-19 had it not suddenly been catapulted to prominence by President Trump's comments. On March 21, for example, the President described it as "one of the biggest game changers in the history

of medicine" and later stated that he was taking the drug himself—the ultimate celebrity endorsement.

On March 28, under pressure from the administration, FDA granted the drug an Emergency Use Authorization (EUA), allowing 29 million doses to be transferred to the Strategic National Stockpile. But my former FDA colleagues Jesse Goodman and Luciana Borio, both of whom have signed off on past EUAs, have attested that the evidence provided for this EUA was below that required for many previous EUAs. (The standard for EUA issuance is that "the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product.") That evidence, as described in FDA's authorization letter, was comprised only of "limited in-vitro and anecdotal clinical data in case series." In other documents, the agency suggested that it also relied upon a French observational study, which was later discredited by its own publisher.

Eventually the scientific process played itself out and the inadequacies of the product to prevent or treat COVID-19 were laid bare. There were several observational studies that variously demonstrated either no benefit for the product or even indicated that mortality rates were higher among those administered the drug as treatment. One study showed that as many as 16% of hospitalized patients prescribed hydroxychloroquine, some concurrently taking other drugs like azithromycin that can also cause arrhythmias, experienced a specific arrhythmia called QT prolongation. Within weeks of the EUA, FDA issued a warning that the product could cause these life-threatening arrhythmias and reminded doctors to only use the drug in

hospitalized settings. Finally, there were two randomized, controlled trials—the gold standard for scientific evidence. The first suggested that the product was ineffective in preventing infection among those exposed to the virus and the second, still unpublished, suggested that it was also ineffective in treating COVID-19 infection itself. On June 15, shortly after the second study was publicized, FDA revoked the EUA. "The totality of scientific evidence currently available," said the agency, "indicate a lack of benefit." At that point, its adverse event reporting database already contained 25 arrhythmia reports in which the patient had died.

What can we learn from this series of events? First, this is a warning not to stray from accepted methods of drug discovery, even in a pandemic. Anecdotes are not evidence. It is the painstaking process of conducting randomized, controlled trials that ultimately produces definitive evidence—even if it is definitive evidence of lack of effectiveness.

Second, while it is tempting to believe, as the President suggested, that infected patients had nothing to lose by taking the drug, that, tragically turned out not to be the case. Life-threatening arrhythmias, as had been predicted, were fairly common, some of them fatal. Even patients without COVID-19 suffered, as those patients needing hydroxychloroquine for its FDA-approved uses (treating lupus and rheumatoid arthritis) had difficulty obtaining the drug amid sudden shortages.

Finally, the President's announcements had a distorting effect upon the overall research effort for COVID-19. It is inconceivable that, left to their own devices, scientists would have designed

over 150 randomized, controlled trials assessing the effectiveness of this drug. How many more promising drugs were left unstudied or understudied as researchers pivoted to address the headlines?

A second repurposed drug that has raised concerns is famotidine, an over-the-counter heartburn drug also known as Pepcid, a seemingly unlikely drug for COVID-19. A physician named Michael Callahan, who was working in China during the early phases of the pandemic, came to believe, based on an informal review, that COVID-19 patients who received the drug died less frequently than those who did not receive the drug. Indeed, an observational study on which Dr. Callahan was a co-author reported a significant reduction in mortality associated with famotidine use. As noted above, such findings in observational studies need to be confirmed in randomized, controlled trials.

Dr. Callahan was also a consultant on the staff of the Health and Human Services Assistant Secretary for Preparedness and Response (ASPR) Dr. Robert Kadlec. Under Dr. Kadlec's direction, Dr. Callahan assisted a pharmaceutical company, Alchem Laboratories, and Northwell Health, a hospital system in the New York City area, to prepare an application for funding to the Biomedical Advanced Research and Development Authority (BARDA), a unit within ASPR, to conduct a randomized, controlled trial of famotidine. Shortly thereafter, Dr. Kadlec ordered BARDA to award a hefty $21 million contract to Alchem, most of which covered Northwell's costs. Senior BARDA officials were cut out of the granting process.

Time will tell whether famotidine will prove effective. But the irregular process by which the contract was granted raises real questions about whether scarce government resources are being committed to the most promising therapeutic candidates.

Two other drugs used for patients with COVID-19 add additional perspectives to this discussion of repurposed drugs. The first, remdesivir, is the only drug so far proved effective against the SARS-CoV-2 virus, but is not a repurposed drug. Rather, it was an unapproved drug with known antiviral activity (not an antimalarial or an anti-heartburn drug) that was demonstrated in a randomized, controlled trial funded by the National Institutes of Health to reduce hospital stay for COVID-19 patients. Whether the second drug, dexamethasone, is a repurposed drug is a matter of definition. It was the subject of significant recent press attention because it appears to be the first drug to reduce mortality in sicker hospitalized patients with COVID-19. (The results have not yet been published.) It has long been approved, but its effectiveness is likely based not on antiviral activity; it is often considered as a general treatment for severe respiratory illness based on its anti-inflammatory activity. What links these two drugs is that their benefits were demonstrated the old-fashioned way: through rigorous randomized, controlled trials. And this experience demonstrates that such trials are feasible and can deliver favorable results even in the urgent setting of a pandemic.

The dexamethasone results are of particular note because they are derived from the same study mentioned above (the RECOVERY Trial) that reported the ineffectiveness of hydroxychloroquine in the treatment of COVID-19. In Britain, where the study was conducted,

there has been better coordination of the COVID-19 research effort, and the resultant RECOVERY trial is very large and able to test multiple candidate therapies simultaneously and rapidly. In contrast, the research effort in the United States has been fragmented and poorly prioritized, resulting in many relatively small studies, often testing the same drugs with some studies struggling to enroll patients.

In conclusion, effective treatments are not generally identified by anecdote, wishful thinking, or questionable contracting practices; they are instead the product of the fair, transparent, and systematic application of the very scientific principles that for decades have delivered so many safe and effective treatments. But when we depart from these approaches, as occurred with both hydroxychloroquine and famotidine, precious time is lost, resources are squandered, and some patients pay with their lives.