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Mitigating risks in prescribing and dispensing chloroquine and hydroxychloroquine for COVID-19

By Sarah M. Hall, Steven A. Block, and Jamar T. King

Sarah M. Hall (sarah.hall@thompsonhine.com) is Senior Counsel in the Washington, DC, Thompson Hine LLP office; **Steven A. Block** (steven.block@thompsonhine.com) is Partner in the Chicago office, and **Jamar T. King** (jamar.king@thompsonhine.com) is an Associate in the Dayton, Ohio, office.

- linkedin.com/in/sarah-m-hall-8379631b/
- linkedin.com/in/stevenablock/
- linkedin.com/in/jamar-king-78675b41/

During his March 19, 2020, press briefing,[1] President Donald Trump called chloroquine and hydroxychloroquine a "game changer" in the battle against COVID-19, the disease caused by the novel coronavirus that has caused a global pandemic. He went on to say, "It's shown...very, very encouraging early results. And we're going to be able to make that drug available almost immediately." The next day on Twitter, he exclaimed that "it" [chloroquine and hydroxychloroquine] must "be put in use IMMEDIATELY."[2]

Chloroquine and hydroxychloroquine are antiviral drugs that have been prescribed for decades. Approved by the U.S. Food and Drug Administration (FDA) to treat malaria, lupus, and rheumatoid arthritis, they have been brought to the forefront of public consciousness through the president's statements and anecdotal evidence repeated on the internet that the drugs are effective in the battle against COVID-19. The public attention on these drugs during the COVID-19 crisis has created serious compliance risks for healthcare organizations and medical professionals that must be addressed.

High demand despite unproven and untested claims

In February and March 2020, reports of French and Chinese studies involving chloroquine and hydroxychloroquine made their way around the internet. In the French study, Professor Didier Raoult, director of France's Research Unit on Emerging Infectious and Tropical Diseases, conducted testing under which 26 COVID-19 patients were treated with a combination of hydroxychloroquine and azithromycin, which is commonly known by one of its trade names, Z-Pak.[3]

After two weeks, 14 patients had been virologically cured. The U.S. Centers for Disease Control and Prevention (CDC) issued a statement on its website that a similar Chinese study "reported that chloroquine treatment of COVID-19 patients had clinical and virologic benefit versus a comparison group, and chloroquine was added as a recommended antiviral for treatment of COVID-19 in China."[4]

However, these and other limited studies with promising results have been sharply criticized as failing to comport with traditional clinical drug development procedures, such as employing test subject randomization and double-blind testing with control groups and placebos. Moreover, a more thorough review of these studies and others shows that their results are inconclusive at best.

For instance, in the French study, "six of the patients treated with hydroxychloroquine had adverse reactions within three days: one died, three were removed from the study when they were transferred to intensive care, one tested negative for the virus and one stopped the treatment because of nausea," *The Intercept* reported.[5] "Those failures were simply dropped from the study's statistics."

And a later Chinese study published in the *Journal of Zhejiang University* found that patients treated with hydroxychloroquine fared no better than patients who received conventional coronavirus treatment.[6] In that study, 30 COVID-19 patients were randomly split into two groups of 15. The first group received conventional coronavirus treatment, while the other received conventional treatment plus 400 milligrams of hydroxychloroquine for seven days. "Fourteen of the non-hydroxychloroquine group tested negative for COVID-19 at the end of the experiment, versus 13 of the people treated with hydroxychloroquine," reported *Newsweek.*

Nevertheless, the American public, understandably desperate for a glimmer of hope in the battle against COVID-19, has focused on these drugs as a possible cure. In one tragic example, an elderly Arizona couple reportedly ingested chloroquine phosphate to prevent contracting the coronavirus. The wife explained that after hearing the president talk about chloroquine and hydroxychloroquine during one of his press briefings, she noticed that chloroquine phosphate was an ingredient in a fish aquarium additive used as treatment against aquatic parasites. She said she thought to herself, "Hey, isn't that the stuff they're talking about on TV?"[7] She and her husband then mixed a small amount of the additive with soda and drank it. They both became severely ill immediately and were soon in critical condition. The wife recovered, but the husband eventually died.

That Arizona couple weren't the only Americans, desperate for a cure, who turned to chloroquine and hydroxychloroquine. In a press conference on March 22, 2020, New York Governor Andrew Cuomo announced that his state, which has been one of the hardest hit as of late March 2020, had acquired 70,000 doses of hydroxychloroquine, 10,000 doses of Zithromax, and 750,000 doses of chloroquine and would begin its own trials.[8] And as of late March 2020, human clinical trials testing chloroquine and hydroxychloroquine were underway in Spain and Norway.[9]

The drugs, even prescribed on-label, pose serious risks

Chloroquine and hydroxychloroquine are not without risks to patients, whether they have COVID-19 or not. The drugs are known to have severe side effects, including heart complications, headaches, dizziness, diarrhea, itchiness, and ear ringing. "So even if chloroquine proves useful in stopping the virus in severe COVID-19 cases," wrote Karen Masterson, the author of *The Malaria Project* and a professor of science journalism at Stony Brook University, "it could prove more dangerous than the virus itself in many people with milder coronavirus infections."[10] Doctors warn that patients with existing heart problems or those who take certain drugs, such as antidepressants that affect heart rhythm, are at risk of a fatal episode of sudden cardiac death.[11]

Pharmacists are under pressure, and patients are at risk

Somewhat surprisingly, despite the inconclusive nature of the available evidence, professional medical providers across the country are writing more and more prescriptions for chloroquine and hydroxychloroquine. CBS News reports that "chloroquine orders spiked 3,000% in March and hydroxychloroquine orders rose 260%."[12] Prescribing chloroquine or hydroxychloroquine to treat COVID-19 is not in and of itself unlawful or unethical, as doctors in the United States are permitted to prescribe drugs off-label and do so in a wide variety of circumstances. However, the sharp increase in demand coupled with the recent publicity have stoked fears from pharmaceutical professionals that physicians may be stockpiling and hoarding the drugs for their patients or, worse yet, for themselves, their family members, and friends. For instance, the executive director of the Ohio

Pharmacists Association told *The Washington Post* that he had heard of cases in which Ohio pharmacists had been asked to fill orders for 1,000 pills and to dispense chloroquine and hydroxychloroquine for prescriptions written by out-of-state physicians[13] —two classic red flags for stockpiling.

Stockpiling and hoarding these drugs have created significant shortage problems for patients who depend on them for on-label use, such as treatment for rheumatoid arthritis and lupus. Hydroxychloroquine is considered the most important treatment for lupus patients. According to the Lupus Foundation of America, "For many people with lupus there are no alternatives to these medications.... [H]ydroxychloroquine or chloroquine are the only methods of preventing inflammation and disease activity that can lead to pain, disability, organ damage, and other serious illness."[14] Noting the reports of shortages, the foundation wrote a letter urging Congress to take legislative action to ensure supplies of chloroquine and hydroxychloroquine remain accessible to lupus patients as demand for the drugs increases amid the search for a COVID-19 cure.[15]

Federal and state governments are rolling out specific prohibitions

In advance of federal action (discussed below), numerous states have taken steps to prevent misuse of the drugs. On March 19, 2020, Idaho became the first state to respond with legal action to curb the run on chloroquine and hydroxychloroquine. The Idaho state pharmacy board imposed an emergency rule requiring prescriptions for chloroquine and hydroxychloroquine to include written diagnoses for illnesses that the drugs have been proven to treat.[16] In addition, the rule limits prescriptions to 14-day supplies. Since then, states including Nevada, Oklahoma, North Carolina, Texas, Ohio, and New York have each implemented similar rules restricting the range of illnesses for which chloroquine and hydroxychloroquine may be prescribed and, in most instances, limiting prescriptions to 14-day supplies.

Five days after Idaho took action, on March 24, 2020, the Ohio attorney general, the Ohio Board of Pharmacy executive director, and the U.S. attorney for the Southern District of Ohio issued a joint statement pledging to hold accountable medical professionals who prescribe the drugs for illegitimate purposes, including through criminal enforcement.[17] "Where we find doctors or others who are abusing their professional licenses to help themselves or associates," wrote the Ohio and federal officials, "we will move swiftly to identify and prosecute any wrongdoing that is a violation of federal or state law."

HHS designates the drugs as subject to federal anti-hoarding rules

On March 23, 2020, three days after he extolled the virtues of chloroquine and hydroxychloroquine, the president signed Executive Order 13910, which delegates his authority under the 1950 Defense Production Act to U.S. Department of Health and Human Services (HHS) Secretary Alex Azar. The Executive Order gives Secretary Azar broad authority to adopt rules and implement measures to "prevent hoarding of health and medical resources necessary to respond to the spread of COVID-19."[18] Under the delegation of authority, Secretary Azar may designate any health or medical supplies, materials, or resources that are necessary to respond to the pandemic as "scarce" or "threatened" materials. Pursuant to that authority, on March 25, 2020, he issued a notice designating chloroquine and hydroxychloroquine drug products as scarce or threatened and subject to federal hoarding prevention measures authorized under the Executive Order and the Defense Production Act.[19]

FDA issues a limited emergency use authorization for the drugs

On March 28, 2020, the FDA issued an emergency use authorization (EUA) for chloroquine and hydroxychloroquine. However, it is limited in scope. Under the EUA, hospitals may request access to the drugs from the Strategic National Stockpile (the federal government's stock of emergency medical supplies located in

warehouses around the country), and the drugs can be distributed to patients who have been hospitalized and tested positive for COVID-19, but for whom a "'clinical trial is not available, or participation is not feasible.'"[20] While it granted the EUA, the FDA cautioned that the drugs "are not FDA-approved for treatment of COVID-19,"[21] recognizing that the medical evidence is still inconclusive as to the drugs' efficacy as a treatment for the virus. In its letter granting emergency approval, the FDA only went so far as to say that "chloroquine phosphate and hydroxychloroquine sulfate *may*be effective in treating COVID-19" (emphasis added).

The EUA does not address longer-term use of the drugs to prevent the coronavirus infection, nor does it address the propriety of medical providers prescribing the drugs off-label. Of note to providers, the EUA does not deem the drugs safe or effective in the fight against COVID-19, and the risks involved in prescribing these drugs persist.

DOJ's heightened enforcement efforts

In the enforcement realm, the U.S. Department of Justice (DOJ) is heading up the federal government's effort to prevent and punish COVID-19-related unlawful conduct. On March 16, 2020, U.S. Attorney General William Barr issued a memorandum directing all federal prosecutors to prioritize the "detection, investigation and prosecution of all criminal conduct related to the current pandemic."[22] The memorandum encourages federal prosecutors to work in conjunction with DOJ officials in Washington, DC, and around the country to focus on COVID-19–related wrongdoing. The attorney general also ordered each U.S. Attorney's Office to appoint a dedicated COVID-19 fraud coordinator.

On March 24, 2020, Attorney General Barr took it a step further by issuing a memorandum announcing the launch of the COVID-19 Hoarding and Price Gouging Task Force,[23] which will work closely with HHS to develop enforcement measures aimed at individuals and companies who are price gouging or hoarding scarce and threatened materials. The memorandum directs each U.S. Attorney's Office to designate a representative to serve on the task force. The task force will ensure that nationwide federal enforcement is uniform, focused, and coordinated. As the COVID-19 pandemic and related economic disruption persist, it is likely that Attorney General Barr will continue to shift DOJ's significant criminal and civil enforcement resources to investigations and prosecutions arising out of the pandemic.

The compliance and enforcement risks when data lasts forever

A federal fraud enforcement sweep has followed every recent major natural disaster in the United States. For the past 15 years, DOJ has coordinated that sweep out of the National Center for Disaster Fraud (NCDF). On March 20, 2020, Attorney General Barr encouraged the public to report COVID-19–related fraud to the NCDF.[24]

The NCDF was established in 2005 when, in the wake of Hurricane Katrina, the federal government poured billions of dollars in federal disaster relief into the Gulf Coast region. As is the norm with natural disasters, many unscrupulous individuals made claims on federal resources to which they were not entitled. With Hurricane Katrina's devastation (and the accompanying fraud) still playing out in 2005, DOJ created the NCDF "to improve and further the detection, prevention, investigation, and prosecution of fraud related to natural and man-made disasters, and to advocate for the victims of such fraud."[25] Following Hurricane Katrina, the NCDF oversaw federal fraud enforcement efforts related to disasters including the Deepwater Horizon oil spill in 2010 and Hurricane Sandy in 2012.

In addition to trying to disrupt fraud in progress, DOJ and its law enforcement partners will look back at conduct occurring during the COVID-19 pandemic—a time of crisis when individuals are not always making the best decisions. Hindsight is 20/20, and the healthcare data generated during the pandemic will last forever, allowing investigators to comb through physician and pharmacy records in the cold light of day, months or years from

now. Additionally, with DOJ looking to suspend the relevant criminal statutes of limitation during the pandemic,[26] the truism that data last forever is even more pertinent.

Although it may be tempting for some medical professionals to stockpile promising COVID-19 treatment drugs, prudence dictates that those with the authority to prescribe or dispense such drugs should resist that temptation, employ the same due diligence they would normally apply, and comply with the various laws and regulations in their respective jurisdictions. Compliance professionals should make legal guidance and resources available to prescribing and dispensing medical professionals and perform appropriate oversight of such practices in larger medical facilities, including hospitals and nursing homes. Keep in mind that the enforcement look-back won't be kind, and all pharmaceutical decision-making should be documented and defensible. Furthermore, the enforcement landscape is changing rapidly, and what may be tolerated today could draw the jaundiced eye of federal and state regulators tomorrow.

History shows that when federal authorities prioritize enforcement efforts in the healthcare field, they focus on several constant themes. First, they will "follow the money" and target those who reap significant profits from illicit activities, such as hoarding or price gouging. Second, they will look to protect vulnerable victims, such as the elderly, those infected with and suffering from COVID-19, and populations that are relatively defenseless, such as nursing home patients. Finally, when identifying those to be held responsible, they will look first at licensed medical professionals such as doctors, nurses, and pharmacists, because DOJ holds them to a higher standard. As the U.S. Sentencing Guidelines state, individuals are to receive more severe punishment if they use their specialized training or skill in the commission of an offense.[27]

Conclusion

Hoarding and inappropriate prescribing of chloroquine and hydroxychloroquine in connection with the COVID-19 pandemic present institutional risks that healthcare compliance professionals are well-advised to understand and control. As the enforcement landscape changes by the day and the pandemic intensifies, so will the pressure on an organization's licensed medical professionals. If your organization has any touch points with these drugs, the time is now to understand and manage your compliance risks.

This article was current as of April 1, 2020. Please contact the authors for more up-to-date information and analysis.

Takeaways

- Chloroquine and hydroxychloroquine have been Food and Drug Administration-approved to treat illnesses such as malaria, rheumatoid arthritis, and lupus for several decades.
- Though the early testing of chloroquine and hydroxychloroquine as a treatment for COVID-19 is promising in limited circumstances, more rigorous studies are necessary to determine the drugs' true efficacy against COVID-19.
- Several states have imposed emergency laws and regulations to prevent the misuse of chloroquine and hydroxychloroquine, including, among other things, limiting prescriptions for the drugs to 14-day supplies.
- The U.S. Department of Health and Human Services designated chloroquine and hydroxychloroquine drug products as scarce or threatened—thereby subject to hoarding prevention measures authorized under federal law.
- The U.S. Department of Justice is prioritizing the investigation and prosecution of wrongdoing related to

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