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Jennifer Bard
Jennifer.bard1@gmail.com

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Cover Page Footnote

Thank you to University of Wyoming College of Law Professor Melissa Ballengee Alexander for her exceptionally helpful and generous comments and to the Public Health and Bioethics SEALS Working Group for their encouragement. Thank you also to the generosity of Dean Laura A. Rosenbury of the University of Florida's Levin College of Law for supporting my visit for the academic year 2019-20 and to Levin College of Law students Pranav S. Patel, B.S., M.P.H. '22, Aleksandra Osterman-Burgess '21, Frankie Berardi '21, and Glen McClain '24, and University of Cincinnati College of Law student Shelbi Shultz '23 for excellent research and editing assistance. Of course, all mistakes in this article are completely my own.

THE PRESIDENT'S REMEDY—WHAT THE HYDROXYCHLOROQUINE STORY TEACHES US ABOUT THE NEED TO LIMIT OFF-LABEL PRESCRIBING POWERS

Jennifer S. Bard[+]

When the history of the first year of the United States Government's response to the COVID-19 virus is written, there is likely to be mention of the still unexplained vehemence with which then president Donald J. Trump made use of his access to social media to promote seldom used anti-malaria drug, hydroxychloroquine, for both the prevention and treatment of COVID-19 despite the active growing opposition of most of the world's scientists, including his own government scientists.

While the use of drugs developed and approved by the FDA for different purposes to combat new diseases, off-label prescribing, is legal in the United States, the intense promotion of two drugs, hydroxychloroquine and ivermectin, cast a light on what has always been a gap in the law between the federal government's power to approve drugs and the states' power over the practice of medicine. In particular, former President Trump's advocacy over twitter and in public appearances of hydroxychloroquine even after it had been found ineffective by the FDA and the efforts of families throughout the country to demand ivermectin, also found by the FDA to be ineffective, be administered to their loved ones being treated for COVID-19 in ICU units highlights the need to address this unsatisfactory compromise. Recent arguments that restricting drug companies from promoting their products off-label are in violation of the first amendment do not take into account social media fueled campaigns that effectively strip FDA of all ability to protect consumers from ineffective and perhaps unsafe drugs so long as it has ever approved them for any reason.

[+] Thank you to University of Wyoming College of Law Professor Melissa Ballengee Alexander for her exceptionally helpful and generous comments and to the Public Health and Bioethics SEALS Working Group for their encouragement. Thank you also to the generosity of Dean Laura A. Rosenbury of the University of Florida's Levin College of Law for supporting my visit for the academic year 2019-20 and to Levin College of Law students Pranav S. Patel, B.S., M.P.H. '22, Aleksandra Osterman-Burgess '21, Frankie Berardi '21, and Glen McClain '24, and University of Cincinnati College of Law student Shelbi Shultz '23 for excellent research and editing assistance. Of course, all mistakes in this article are completely my own.

INTRODUCTION

The COVID-19 pandemic has caused millions of deaths around the world and challenged the medical and scientific community to develop safe and effective methods of preventing and treating this new disease. The speed with which they

have met this challenge is exceptional. But equally exceptional are the efforts of physicians and health care workers who, starting in December 2019, had to act immediately to take care of the first thousands, then millions of people who began to fill hospitals. They had no other choice than to repurpose whatever available medications might plausibly stop the virus' reproduction. In the United States, this experimentation was facilitated by the compromise struck between the federal government, which exercises power over the approval of drugs, and the practice of medicine.

When the history of the first year of the United States Government's response to the COVID-19 virus is written, there is likely to be mention of the still unexplained vehemence with which then-president Donald J. Trump made use of his access to social media to promote seldom-used anti-malaria drug, hydroxychloroquine, for both the prevention and treatment of COVID-19 despite the active growing opposition of most of the world's scientists, including his own government scientists.[1] He did so in a context where there was no safe and effective treatment so that doctors around the world had to use the drugs at hand while awaiting the development of ones fit for this purpose.[2] While the use of drugs developed and approved for different purposes to combat new diseases is legal in the United States, President Trump's advocacy provides an opportunity for a closer look at the larger phenomena of "off-label" prescribing, which represents a compromise between the U.S. Food and Drug Administration's (FDA) statutory authority to preauthorize new drugs and the individual states' plenary power recognized by the 10th Amendment to regulate the practice of medicine within their borders.[3] Within the context of this compromise, the practice of repurposing drugs already approved by the FDA is called using them "off-label" because the FDA's statutory authority to preauthorize drugs is structured in terms of prohibiting their sale without an FDA approved "label."[4] As a result, any state licensed health care provider has the

1. *See infra* for a more detailed timeline of statements made by federal government employees following specific endorsements by President Trump, such as this statement of Stephen Hahn, then commissioner of the FDA in late July after President Trump doubled down on his support for the drug in spite of medical evidence questioning its efficacy as a treatment for COVID-19 and raising concerns over possible side effects. "We had data that when this drug was combined with others, there was some risk associated with that. But the question you're asking me is a decision between a doctor and a patient." Tal Axelrod, *FDA Chief: Hydroxychloroquine Is a Decision Between Doctor and Patient*, THE HILL (July 30, 2020, 8:25 AM), https://thehill.com/policy/healthcare/509733-fda-chief-hydroxychloroquine-use-a-decision-between-doctor-and-patient.

2. Joseph M. Geskey, *Off-Label Prescribing in the Era of COVID-19*, MED. ECON. (Apr. 14, 2020), https://www.medicaleconomics.com/med-ec-blog/label-prescribing-era-covid-19.

3. Amirahmad Shojaei & Pooneh Salari, *COVID-19 and Off Label Use of Drugs: An Ethical Viewpoint*, 28 DARU J. PHARM. SCIS. 789, 789 (2020) ("There is no specific effective treatment and optimized supportive care is indicated for the patients.").

4. For a concise and helpful overview of the current regulatory scene and the legal debate surrounding it, *see* Elizabeth Richardson, *Off-Label Drug Promotion*, HEALTH AFFS. (June 30, 2016), https://www.healthaffairs.org/do/10.1377/hpb20160630.920075/full/. For more information

freedom to treat any patient for any condition with any FDA approved drug regardless of the purpose for which the drug was originally authorized.[5]

The Article proceeds as follows: Part I tells the story of President Trump's promotion of hydroxychloroquine and the effect it had on sales and use of the product. Part II outlines the legal framework of off-label prescribing, Part III looks at criticisms of and justifications for off label prescribing, Part IV looks at how the patient safety issues inherent in off-label prescribing have been obscured by concerns about the First Amendment rights of pharmaceutical companies to promote their product, and Part V concludes by proposing some solutions justified by likely continued use of off-label products to treat COVID-19.

I. THE TALE OF PRESIDENT DONALD J. TRUMP'S PROMOTION OF HYDROXYCHLOROQUINE: SETTING THE SCENE

Along with the sickness, death, and economic disaster that the novel COVID-19 virus has brought to the world has been the unprecedented spectacle of a President of the United States taking on the role of spokesman for two little-used anti-malaria drugs, hydrochloroquine, marketed under the name Plaquenil, and chloroquine—collectively referred to as hydroxychloroquine—that are among the many medications being tried to combat a deadly new virus for which there was no FDA approved treatment or vaccine.[6]

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on what the FDA requires as part of a drug label, *see Prescription Drug Labeling Resources*, U.S. FOOD & DRUG ADMIN. (Oct. 7, 2021), https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources.

5. Elizabeth Richardson, *Off-Label Drug Promotion*, HEALTH AFFS. (June 30, 2016), https://www.healthaffairs.org/do/10.1377/hpb20160630.920075/full/.

6. *COVID Data Tracker: United States at a Glance*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html (last visited July 26, 2020); the excess deaths count gives a more accurate death count attributable to COVID-19 at any point in time. *See Excess Deaths Associated with COVID-19*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm (last visited July 8, 2020)*; COVID-19's Historic Impact, in the U.S. and Abroad*, JOHN HOPKINS UNIV. (Apr. 16, 2020), https://hub.jhu.edu/2020/04/16/coronavirus-impact-on-european-american-economies/; *About COVID-19*, WASH. UNIV. IN ST. LOUIS, https://emergency.wustl.edu/coronavirus-disease-covid-19/covid-19-faqs/about-covid 19/#:~:text=COVID%2D19%20is%20a,to%20more%20serious%20diseases (last visited May 28, 2020). Some of the mosquitos which carry Malaria have become resistant to its active ingredient chloroquine. *See Drug Resistance in the Malaria-Endemic World*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/malaria/malaria_worldwide/reduction/drug_resist (last visited July 1, 2020). Although the President frequently capitalizes it, "hydroxychloroquine sulfate" is actually the generic name for the drug manufactured by Sanofi as Plaquenil. *See* SANOFI-AVENTIS CANADA INC., PRODUCT MONOGRAPH INCLUDING PATIENT MEDICATION INFORMATION: PLAQUENIL (2021), http://products.sanofi.ca/en/plaquenil.pdf ("PLAQUENIL (hydroxychloroquine sulfate tablets) belongs to the 4-aminoquinoline class. PLAQUENIL has been beneficial for patients with rheumatoid arthritis and lupus erythematosus, especially chronic discoid lupus. The exact mode of action in controlling these diseases is unknown. The action of this compound against malarial parasites is similar to that of chloroquine phosphate."); *see* Sanjai Sinha, *Hydroxychloroquine*,

A. Documenting the Promotion During President Trump's Term in Office

President Trump's first public mention of the drug was in a tweet dated March 21, 2020, stating "HYDROXYCHLOROQUINE & AZITHROMYCIN, taken together, have a real chance to be one of the biggest game changers in the history of medicine.[7] The FDA has moved mountains-Thank You!"[8] The "mountains" he referred to were the issuing of an "emergency use authorization"[9] ("EUA") that allowed the drug's addition to the national stockpile and limited approval for its use in hospitalized patients.[10] The Trump Twitter Archive notes three different tweets mentioning hydroxychloroquine on March 22–23, 2020, two of which are retweets of the result of a French study.[11]

DRUGS.COM (July 2, 2020), https://www.drugs.com/hydroxychloroquine.html ("Hydroxychloroquine is a quinoline medicine used to treat or prevent malaria, a disease caused by parasites that enter the body through the bite of a mosquito. Malaria is common in areas such as Africa, South America, and Southern Asia. This medicine is not effective against all strains of malaria. Hydroxychloroquine is not effective against all strains of malaria, or against malaria in areas where the infection has been resistant to a similar drug called chloroquine. Hydroxychloroquine is also used to treat symptoms of rheumatoid arthritis and discoid or systemic lupus erythematosus."). *See also* SANOFI-AVENTIS CANADA INC., PRODUCT MONOGRAPH INCLUDING PATIENT MEDICATION INFORMATION: PLAQUENIL 4 (2021), http://products.sanofi.ca/en/plaquenil.pdf; Joseph M. Geskey, *Off-Label Prescribing in the Era of COVID-19*, MED. ECON. (Apr. 14, 2020), https://www.medicaleconomics.com/view/label-prescribing-era-covid-19 ("Despite no evidence-based literature supporting a standard-of-care for coronavirus infections, many providers are prophylactically prescribing medications like Hydroxychloroquine and Azithromycin in the hope that it will arrest the virus from causing a 'cytokine storm.'"); *see also* Steve Almond, *Why America Can't Stop COVID-19*, WBUR (May 13, 2020), https://www.wbur.org/cognoscenti/2020/05/13/coronavirus-donald-trump-gop-steve-almond.

7. Tamara Keith & Malaka Gharib, *A Timeline of Coronavirus Comments From President Trump and WHO*, NPR (Apr. 15, 2020, 5:33 PM), https://www.npr.org/sections/goatsandsoda/2020/04/15/835011346/a-timeline-of-coronavirus-comments-from-president-trump-and-who; Donald J. Trump (@realDonaldTrump), TRUMP TWITTER ARCHIVE V2 (Mar. 21, 2020, 10:13 AM), https://www.thetrumparchive.com/.

8. Donald J. Trump (@realdonaldtrump), TRUMP TWITTER ARCHIVE V2 (Mar. 21, 2020, 10:13 AM), https://www.thetrumparchive.com/; *Coronavirus (COVID-19) Update: Daily Roundup March 30, 2020*, U.S. FOOD & DRUG ADMIN. (Mar. 30, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-30-2020.

9. Letter from Denise M. Hinton, Chief Scientist, FDA, to Rick Bright, Dir., Biomedical Advanced Rsch. and Dev. Auth., U.S. Dep't Health and Hum. Servs. (Mar. 28, 2020), https://www.fda.gov/media/136534/download (last visited July 21, 2020) (currently marked "Revoked").

10. Jennifer S. Bard, *Human Subjects Research in Emergencies: The Texas Nursing Home 'Study' (Part II)*, HARV. L. SCH.: BILL OF HEALTH (Apr. 27, 2020), https://blog.petrieflom.law.harvard.edu/2020/04/27/human-subjects-research-hydroxychloroquine-texas-covid19/#more-28705.

11. Donald J. Trump (@realdonaldtrump), TRUMP TWITTER ARCHIVE V2 (Mar. 21, 2020, 10:13 AM), https://www.thetrumparchive.com/; Donald J. Trump (@realdonaldtrump), TRUMP TWITTER ARCHIVE V2 (Mar. 21, 2020, 12:16 PM), https://www.thetrumparchive.com/; Donald J. Trump (@realdonaldtrump), TRUMP TWITTER ARCHIVE V2 (Mar. 22, 2020, 12:15 AM), https://www.thetrumparchive.com/; Kacper Niburski & Oskar Niburski, *Impact of Trump's*

At that time, no drug, including hydroxychloroquine, had FDA approval for sale in the United States for the treatment of COVID-19. The EUA had the effect of converting hydroxychloroquine from unapproved for COVID-19 to approved in the specific circumstances detailed in the EUA. Not only was the drug approved for emergency use, it was added to the Strategic National Stockpile ("SNS"), a federally managed program to maintain medicines, medical devices, like ventilators, and medical supplies in case of national emergency.[12] The significance of adding hydroxychloroquine to the stockpile was so that "[t]he U.S. Department of Health and Human Services (HHS) . . . [could] accept[] . . . 30 million doses" donated by several of the companies which manufactured drugs containing hydroxychloroquine sulfate.[13]

For about a month, much to the concern of physicians treating COVID-19 patients, Americans were treated to the extraordinary sight of the President of the United States speaking to them in live news conferences and then from the White House to urge them to ask to be prescribed a specific drug.[14] At a March 23, 2020, press briefing, the President announced that he was "a big fan" of the drug's promise against COVID-19 even as he acknowledged that it needed to be tested first.[15] On June 3, 2020, President Trump announced that he, himself, had taken a two week preventive course of hydroxychloroquine.[16]

Promotion of Unproven COVID-19 Treatments and Subsequent Internet Trends: Observational Study, 22 J. MED. INTERNET RSCH. (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7685699/?.

12. *Public Health Emergency: Strategic National Stockpile*, U.S. DEP'T OF HEALTH AND HUM. SERVS. (last reviewed Aug. 9, 2021), https://www.phe.gov/about/sns/Pages/default.aspx.

13. In particular, the drugs were "donated by Sandoz, the Novartis generics and biosimilars division, and one million doses of Resochin (medical grade chloroquine phosphate) donated by Bayer Pharmaceuticals . . . ." *HHS Accepts Donations of Medicine to Strategic National Stockpile as Possible Treatments for COVID-19 Patients*, U.S. DEP'T OF HEALTH AND HUM. SERVS. (Mar. 29, 2020), https://www.hhs.gov/about/news/2020/03/29/hhs-accepts-donations-of-medicine-to-strategic-national-stockpile-as-possible-treatments-for-covid-19-patients.html.

14. Peter Baker et al., *Trump's Aggressive Advocacy of Malaria Drug for Treating Coronavirus Divides Medical Community*, N.Y. TIMES (Apr. 6, 2020), https://www.nytimes.com/2020/04/06/us/politics/coronavirus-trump-malaria-drug.html.; Philip Bump, *Trump's Promotion of Hydroxychloroquine Is Almost Certainly About Politics, Not Profits*, WASH. POST (Aug. 7, 2020), https://www.washingtonpost.com/politics/2020/04/07/trumps-promotion-hydroxychloroquine-is-almost-certainly-about-politics-not-profits/.

15. Tamara Keith & Malaka Gharib, *A Timeline of Coronavirus Comments From President Trump and WHO*, NPR (Apr. 15, 2020, 5:33 PM), https://www.npr.org/sections/goatsandsoda/2020/04/15/835011346/a-timeline-of-coronavirus-comments-from-president-trump-and-who; Donald J. Trump (@realDonaldTrump), TRUMP TWITTER ARCHIVE V2 (Mar. 21, 2020, 10:13:08–09 AM), https://www.thetrumparchive.com/; Libby Cathey, *Timeline: Tracking Trump Alongside Scientific Developments on Hydroxychloroquine*, ABC NEWS (Aug. 8, 2020, 8:12 AM), https://abcnews.go.com/Health/timeline-tracking-trump-alongside-scientific-developments-hydroxychloroquine/story?id=72170553.

16. Katie Rogers & Lawrence K. Altman, *Trump 'Remains Healthy' After Taking Hydroxychloroquine, His Doctor Says*, N. Y. TIMES (June 3, 2020), https://www.nytimes.com/2020/06/03/us/politics/trump-physical-hydroxychloroquine.html.

The President's unusual advocacy for a specific drug attracted the attention of the media, which soon found many sources tempering enthusiasm by pointing to both the lack of evidence that hydroxychloroquine was effective in combatting COVID-19 and, more seriously, that there were significant safety concerns.[17] Not only was the President claiming hydroxychloroquine was a cure for COVID-19, he also touted it as a preventative, even though no clinical trials had found any such evidence.[18] In late April 2020, the announcement by a director of a nursing home in Texas that he had obtained hydroxychloroquine through a political connection and administered it as "an experiment" to 39 patients sick with COVID-19 was met with serious concern from ethicists, scientists, and regulators.[19] As if the story was not interesting enough, on April 22, 2020, the *New York Times* reported that a former HHS official was going to testify as a whistleblower to Congress based on retaliation against him for opposing the addition of hydroxychloroquine to the national stockpile.[20] Dr. Rick Bright testified that he was pressured to direct money toward hydroxychloroquine, one of several "potentially dangerous drugs promoted by those with political connections."[21] Responding directly to Dr. Bright's testimony in a tweet on May 18, 2020 which was "liked" by 82.4K Twitter users, retweeted by 26.6K, and commented on by 11.8K, President Trump said "The so-called HHS Whistleblower was against HYDROXYCHLOROQUINE. Then why did he make, and sign, an emergency use authorization?"[22] Perhaps to bolster his earlier advocacy and negate Dr. Bright's testimony, on May 18, 2020 the President announced to a briefing room of reporters while on live television

17. Oliver Milman, *Trump Touts Hydroxychloroquine as a Cure for Covid-19. Don't Believe the Hype*, THE GUARDIAN (Apr. 6, 2020, 2:33 PM), https://www.theguardian.com/science/2020/apr/06/coronavirus-cure-fact-check-hydroxychloroquine-trump (reviewing the President's advocacy for the drug and noting that "Trump has been repeatedly contradicted by public health experts including his own top infectious diseases adviser, Dr Anthony Fauci, who has warned that there is only 'anecdotal evidence' that the drugs could be helpful").

18. Robin E. Ferner & Jeffrey K. Aronson, *Hydroxychloroquine for COVID-19: What Do The Clinical Trials Tell Us?*, CTR. FOR EVIDENCE BASED MED. (Apr. 14, 2020), https://www.cebm.net/covid-19/hydroxychloroquine-for-covid-19-what-do-the-clinical-trials-tell-us/.

19. For an account of the events at the Texas Nursing Home based on information available in April 2020, *see* Jennifer S. Bard, *Human Subjects Research in Emergencies: The Texas Nursing Home "Study" (Part II),* HARV. L. SCH.: BILL OF HEALTH (Apr. 27, 2020), https://blog.petrieflom.law.harvard.edu/2020/04/27/human-subjects-research-hydroxychloroquine-texas-covid19/#more-28705.

20. Michael D. Shear & Maggie Haberman, *Health Dept. Official Says Doubts on Hydroxychloroquine Led to His Ouster*, N.Y. TIMES (Aug. 9, 2021), https://www.nytimes.com/2020/04/22/us/politics/rick-bright-trump-hydroxychloroquine-coronavirus.html; *see also* Laurel Wamsley, *Rick Bright, Former Top Vaccine Scientist, Files Whistleblower Complaint*, NPR (May 5, 2020, 7:03 PM), https://www.npr.org/sections/coronavirus-live-updates/2020/05/05/850960344/rick-bright-former-top-vaccine-scientist-files-whistleblower-complaint.

21. *Id.*

22. Donald J. Trump (@realDonaldTrump), TRUMP TWITTER ARCHIVE V2 (May 18, 2020, 10:44 AM), https://twitter.com/realdonaldtrump/status/1262393595560067073.

that he, himself was taking the drug as a preventative.[23] This triggered a press request for a statement from the president's physician which, when it appeared, did not state directly that the President had ingested the drug so much as it stated the President's medical team "concluded the potential benefits from treatment outweighed the relative risks."[24] On May 18, 2020 in which he responded to an article criticizing his taking the drug by Neil Cavuto, the President retweeted, "CAVUTO IS AN IDIOT. THIS DRUG DOES NOT KILL PEOPLE."[25]

On May 24, the President announced in an interview with Sharyl Attkisson that he was no longer taking the drug.[26] On May 25, the World Health Organization announced that it was suspending its global trial of hydroxychloroquine because of "safety" concerns.[27]

But as quickly as hydroxychloroquine rose to prominence, its fall from favor was just as fast. On June 15, 2020, the FDA revoked the EAU and removed it from the national stockpile.[28]

Information about hydroxychloroquine continues to develop. A study in the prestigious British journal, the Lancet, which reported that hydroxychloroquine was linked to increased risk of death in COVID-19 patients, was retracted.[29] Yet

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23. Anne Gearan et al., *Trump Says He is Taking Hydroxychloroquine to Protect Against Coronavirus, Dismissing Safety Concerns*, WASH. POST (May 18, 2020), https://www.washingtonpost.com/politics/trump-says-he-is-taking-hydroxychloroquine-to-protect-against-coronavirus-dismissing-safety-concerns/2020/05/18/7b8c928a-9946-11ea-ac72-3841fcc9b35f_story.html.

24. *Trump's Physician Releases Letter on President Taking Hydroxychloroquine*, CNN (May 18, 2020, 8:47 PM), https://www.cnn.com/2020/05/18/politics/trump-physician-on-hydroxychloroquine/index.html.

25. Donald J. Trump (@realdonaldtrump), TRUMP TWITTER ARCHIVE (May 18, 2020), http://trumptwitterarchive.com/archive.

26. *Full Measure: May 24, 2020 - Interview with the President*, FULL MEASURE (May 24, 2020), http://fullmeasure.news/news/full-episodes/full-measure-may-24-2020-interview-with-the-president ("Sharyl: Many people are taking the government guidance on the anti-malaria drug, hydroxychloroquine to basically ward them off of using it and trying it. On the other hand, there are current experiments going on by National Institutes of Health and academic institutions, including for preventive uses possibly, you're finishing your two-week course of hydroxychloroquine, correct? President Trump: Finished, just finished, yeah.").

27. *Coronavirus: WHO Halts Trials of Hydroxychloroquine Over Safety Fears*, BBC NEWS (May 25, 2020), https://www.bbc.com/news/health-52799120.

28. *EUA Hydroxychloroquine Sulfate Health Care Provider Fact Sheet*, U.S. FOOD & DRUG ADMIN. (posted Apr. 27, 2020, revoked June 15, 2020), https://www.fda.gov/media/136537/download. For contemporary retrospective of the time between the FDA's issuance and withdrawal of the EAU, *see* Sheryl Gay Stolberg, *A Mad Scramble to Stock Millions of Malaria Pills, Likely for Nothing*, N.Y. TIMES (June 16, 2020), https://www.nytimes.com/2020/06/16/us/politics/trump-hydroxychloroquine-coronavirus.html. *Coronavirus: WHO Halts Trials of Hydroxychloroquine Over Safety Fears*, BBC NEWS, (May 25, 2020), https://www.bbc.com/news/health-52799120 (discussing the suspension of trials of hydroxychloroquine in several countries).

29. Marisa Fernandez, *Update: Study Linking Hydroxychloroquine to Increased Death is Retracted*, AXIOS (May 22, 2020), https://www.axios.com/hydroxychloroquine-coronavirus-increase-death-e530f64b-feb2-47bc-8d4b-6d98f79ed5cc.html.

former FDA Commissioner Scott Gottlieb downplayed the significance of the retraction stating that while the study might be flawed, "hydroxychloroquine 'definitively' does not work as a coronavirus treatment."[30] On July 6, President Trump cited the Detroit study to complain that "HYDROXYCHLOROQUINE cut the death rate in certain sick patients very significantly" but "The Dems disparaged it for political reasons (me!). Disgraceful" and he concluded by exhorting @US_FDA to "Act now" to reissue the emergency use authorization.[31] On July 10, *The Washington Post* reported that "White House trade adviser Peter Navarro is leading a Trump administration effort to demand the Food and Drug Administration reverse course and grant a second emergency authorization for the antimalarial drug hydroxychloroquine . . . ."[32] The President's advocacy continued throughout the summer of 2020.[33] On July 28, 2020, more than a month after the FDA had revoked its EUA, he posted a video of a group of doctors declaring that "hydroxychloroquine is a coronavirus 'cure' and that masks are unnecessary."[34] When confronted with statements by Dr. Fauci on July 29 denouncing the group as "peddling coronavirus disinformation," the President reasserted his faith in hydroxychloroquine saying that, "I happen to think it works in the early stages . . . ."[35]

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30. Ursula Perano, *Former FDA Head Scott Gottlieb: "We Can Definitively Say Hydroxychloroquine Doesn't Work"*, AXIOS (July 29, 2020), https://www.axios.com/hydroxychloroquine-coronavirus-scott-gottlieb-trump-a7b60575-91db-4239-8c86-59b993c55358.html.

31. Donald J. Trump (@realdonaldtrump), TRUMP TWITTER ARCHIVE V2 (July 6, 2020, 10:46 PM), http://trumptwitterarchive.com/archive (last visited July 26, 2020); Aaron Blake, *Trump is Making it Harder and Harder to Escape Blame on the Coronavirus*, WASH. POST (July 8, 2020), https://www.washingtonpost.com/politics/2020/07/08/trump-is-making-it-harder-harder-escape-blame-coronavirus/.

32. "Navarro, armed with a new study that he says shows the drug's effectiveness, is being cheered on by President Trump, who has long touted the drug as a 'game changer.'" *See* Laurie McGinley & Josh Dawsey, *Touting Criticized Study, White House Presses FDA to Authorize Hydroxychloroquine – Again*, WASH. POST (July 10, 2020), https://www.washingtonpost.com/health/2020/07/10/peter-navarro-hydroxychloroquine-coronavirus/.

33. Jason Easley, *Trump Self-Destructs and Attacks CNN and MSNBC While Defending Hydroxychloroquine*, POLITICS USA (July 29, 2020), https://www.politicususa.com/2020/07/29/trump-cnn-msnbc-hydroxychloroquine.html.

34. Justin Baragona, *Dr. Fauci Rails Against COVID Disinformation Video Featuring Demon Sperm Doctor*, DAILY BEAST (July 29, 2020, 2:53 PM), https://www.thedailybeast.com/dr-fauci-rails-against-covid-disinformation-video-featuring-demon-sperm-doctor; Lev Facher et al., *FDA revokes emergency use ruling for hydroxychloroquine, the drug touted by Trump as a Covid-19 therapy*, STAT (2020), https://www.statnews.com/2020/06/15/fda-revokes-hydroxychloroquine/ (last visited Apr. 8, 2022).

35. *Id.*; Quint Forgey & Caitlin Oprysko, *"I Happen to Think it Works": Trump Doubles Down on Hydroxychloroquine*, POLITICO (July 28, 2020, 7:12 PM), https://www.politico.com/news/2020/07/28/fauci-trump-ineffective-coronavirus-treatment-383809.

B. Immediate Consequences of Presidential Advocacy

President Trump's endorsement of hydroxychloroquine influenced many to seek it out.[36] An article published on March 25, 2020 quoted executive director of the Massachusetts Independent Pharmacists Association, Todd Brown, who told a reporter that "[o]ur members are definitely seeing more demand for this medication and possibly some people trying to hoard the medication."[37] Brown is further attributed as saying that "it appears the hoarders included doctors and dentists who are writing prescriptions for themselves or family members."[38] His perception of increased prescriptions was supported by the executive director of the National Association of Boards of Pharmacy, who said that "[b]ased on reports we see from the states, pharmacists have a fairly good idea that what they're seeing is prescribers prescribing for themselves and their families and stockpiling these medications rather than prescribing for patients."[39] She further noted that six states had already "taken steps to limit inappropriate prescriptions for hydroxychloroquine and preserve supplies for patients who take the medicine as approved."[40]

Another, tragic sign that the President's message was effective came from the wife of a man in California who died because they took, on the President's advice, what they believed to be a similar sounding component used to clean fish tanks which would work to prevent COVID-19.[41]

On April 14, 2020, Dr. Joseph M. Geskey wrote a column in *Medical Economics* that cited President Trump's tweets and sought to advise physicians of "potential pitfalls" that they "need to know about" in prescribing off-label. He empathized, however, with their "understandable bias toward action" and their adoption of the slogan, "Don't just stand there. Do something."[42]

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36. *See* Martha Bebinger, *Why Hoarding of Hydroxychloroquine Needs to Stop*, WBUR (Mar. 25, 2020), https://khn.org/news/why-hoarding-of-hydroxychloroquine-needs-to-stop/ ("Pharmacists are seeing an increase in requests and prescriptions for them in instances where it's not clear why the patient needs it at this time.").

37. *Id.*

38. *Id.*

39. *Id.*

40. *Id.*

41. Scott Neuman, *Man Dies, Woman Hospitalized After Taking Form Of Chloroquine to Prevent COVID-19*, NPR (Mar. 24, 2020, 4:20 AM), https://www.npr.org/sections/coronavirus-live-updates/2020/03/24/820512107/man-dies-woman-hospitalized-after-taking-form-of-chloroquine-to-prevent-covid-19; *see also* Erika Edwards & Vaughn Hillyard, *Man Dies After Taking Chloroquine in an Attempt to Prevent Coronavirus*, NBC NEWS (Mar. 23, 2020, 5:53 PM), https://www.nbcnews.com/health/health-news/man-dies-after-ingesting-chloroquine-attempt-prevent-coronavirus-n1167166 ("The man's wife told NBC News she'd watched televised briefings during which President Trump talked about the potential benefits of chloroquine.").

42. Joseph M. Geskey, *Off-Label Prescribing in the Era of COVID-19*, MED. ECONS. (Apr. 14, 2020), https://www.medicaleconomics.com/view/label-prescribing-era-covid-19.

Soon, evidence began to emerge of a rise in prescriptions sparking a run on the drug.[43] People seeking their regular prescriptions for conditions such as Lupus became concerned.[44] Further evidence emerged that many of the prescriptions were written by doctors outside of those who could be expected to treat COVID-19 patients, such as urologists, dermatologists, and podiatrists.[45] More to the point, evidence emerged that they were writing prescriptions for themselves and their friends.[46] Predictably, supplies of hydroxychloroquine ran short and people who depended on it had difficulty filling their prescriptions.[47] The shortage became so concerning that the American Medical Association (AMA) felt it necessary to call "for a stop to any inappropriate prescribing and ordering of medications, including chloroquine or hydroxychloroquine, and appealing to physicians and all health care professionals to follow the highest

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43. Ariana Eunjung Cha & Laurie McGinley, *Antimalarial Drug Touted by President Trump is Linked to Increased Risk of Death in Coronavirus Patients, Study Says*, WASH. POST (May 22, 2020), https://www.washingtonpost.com/health/2020/05/22/hydroxychloroquine-coronavirus-study/.

44. Maya L. Harris, *Some Patients Really Need the Drug That Trump Keeps Pushing*, THE ATLANTIC (Apr. 12, 2020), https://www.theatlantic.com/ideas/archive/2020/04/save-hydroxychloroquine-people-like-me/609865/; *FDA Recognizes Hydroxychloroquine and Chloroquine Shortages*, LUPUS FOUND. OF AMER. (Mar. 31, 2020), https://www.lupus.org/news/fda-recognizes-hydroxychloroquine-and-chloroquine-shortages ("The agency is working with manufacturers to assess their supplies and is actively evaluating market demand for patients dependent on hydroxychloroquine and chloroquine for treatment of malaria, lupus and rheumatoid arthritis. *All manufacturers are ramping up production, and the agency's webpage displays current availability*.").

45. Further research will tell us more about what was actually happening. The fact that there is a requirement to indicate on a prescription the condition of the patient for whom it is written means that it is difficult to know if these prescriptions were for patients showing different manifestations of COVID-19. *See* Ellen Gabler & Michael H. Keller, *Prescriptions Surged as Trump Praised Drugs in Coronavirus Fight*, N.Y. TIMES (Oct. 22, 2020), https://www.nytimes.com/2020/04/25/us/coronavirus-trump-chloroquine-hydroxychloroquine.html; *see also* Jinoos Yazdany & Alfred H.J. Kim, *Use of Hydroxychloroquine and Chloroquine During the COVID-19 Pandemic: What Every Clinician Should Know*, ANNALS OF INTERNAL MED. (June 2, 2020), https://www.acpjournals.org/doi/10.7326/M20-1334 ("Hoarding by health professionals for themselves and their friends or family is already occurring, but state governments and pharmacy boards have started to institute strict utilization policies to prevent further HCQ overutilization.").

46. *Doctors are Prescribing Drug that May Help Treat Coronavirus for Family and Friends: "Unethical and Selfish,"* CBS NEWS (Mar. 26, 2020, 8:43 AM), https://www.cbsnews.com/news/coronavirus-treatment-drug-hydroxychloroquine-doctor-prescription-family-friends/.

47. The shortage seems to be easing as of July 1, 2020. *See* EJ Dickson, *Thanks to Trump, There's a Hydroxychloroquine Shortage for People Who Need It*, ROLLING STONE (Apr. 6, 2020, 4:09 PM), https://www.rollingstone.com/culture/culture-news/hydroxychloroquine-trump-coronavirus-covid19-pandemic-miracle-drug-978994/; *see also State Action on Hydroxychloroquine and Chloroquine Access*, LUPUS FOUND. OF AM. (last accessed July 30, 2020), https://www.lupus.org/advocate/state-action-on-hydroxychloroquine-and-chloroquine-access; Ken Alltucker, *'Medication I can't live without': Lupus Patients Struggle to Get Hydroxychloroquine, In Demand for COVID-19*, USA TODAY (Apr. 19, 2020, 12:22 PM), https://www.usatoday.com/story/news/health/2020/04/18/hydroxychloroquine-coronavirus-creates-shortage-lupus-drug/5129896002/.

standards of professionalism and ethics."[48] Evidence of hoarding continues to emerge.[49]

The President's comments also affected clinical trials for other potential treatments. In some cases, patients refused to forgo the option of receiving hydroxychloroquine.[50] More generally, so long as the FDA endorsed hydroxychloroquine as a treatment, it was necessary to include it in comparative studies of other potential treatments which may have had the effect of magnifying even very modest effects.[51] Even worse, it is necessary to continue testing hydroxychloroquine, long after the findings that have caused many countries to prematurely end trials.[52] Finally, if that were not damage enough, it may be necessary to conduct trials for new drugs comparing them to hydroxychloroquine.[53]

Over time, the President's advocacy of hydroxychloroquine in the face of growing scientific evidence that it did not work became a proxy for supporting President Trump against a "deep state" conspiracy mounted against him.[54]

C. Effect of Advocacy After President Trump Left Office

Neither President Trump's loss of the election to Joe Biden nor ban from Twitter has dampened the enthusiasm of those who supported him for the use of

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48. *Boards of Pharmacy and Other Actions Relating to COVID-19 Prescribing*, AM. MED. ASS'N (Apr. 27, 2020, 9:00 AM), https://www.ama-assn.org/system/files/2020-04/board-of-pharmacy-covid-19-prescribing.pdf; *Joint Statement on Ordering, Prescribing or Dispensing COVID-19 Medications*, AM. MED. ASS'N (Apr. 17, 2020), https://www.ama-assn.org/delivering-care/public-health/joint-statement-ordering-prescribing-or-dispensing-covid-19; Ellen Gabler, *States Say Some Doctors Stockpile Trial Coronavirus Drugs, for Themselves*, N.Y. TIMES (Apr. 9, 2020), https://www.nytimes.com/2020/03/24/business/doctors-buying-coronavirus-drugs.html.

49. Jacquie Lee, *Virus Drug Hoarding Prompts Calls for Accessible Data, Supplies*, BLOOMBERG L. (July 17, 2020, 5:26 AM), https://news.bloomberglaw.com/pharma-and-life-sciences/virus-drug-hoarding-prompts-calls-for-accessible-data-supplies.

50. Sara Talpos, *Is Hydroxychloroquine Making COVID-19 Clinical Trials Harder?*, MEDSCAPE (Apr. 15, 2020), https://www.medscape.com/viewarticle/928719.

51. *NIH Begins Clinical Trial of Hydroxychloroquine and Azithromycin to Treat COVID-19*, NAT'L INSTS. HEALTH (May 14, 2020), https://www.nih.gov/news-events/news-releases/nih-begins-clinical-trial-hydroxychloroquine-azithromycin-treat-covid-19.

52. Marie McCullough, *Hydroxychloroquine is the Most Disappointing, Disavowed Drug that Researchers Keep Studying for COVID-19*, MED. XPRESS (July 6, 2020), https://medicalxpress.com/news/2020-07-hydroxychloroquine-disappointing-disavowed-drug-covid-.html.

53. Matthew Herper & Erin Riglin, *Data Show Panic and Disorganization Dominate the Study of Covid-19 Drugs*, STAT (July 6, 2020), https://www.statnews.com/2020/07/06/data-show-panic-and-disorganization-dominate-the-study-of-covid-19-drugs/.

54. *Hydroxychloroquine & The Hybrid War on Trump's America*, ONEWORLD PRESS (Apr. 7, 2020), http://oneworld.press/?module=articles&action=view&id=1393 ("It obviously can't be known for sure, but there are serious grounds for speculating that the topic of Hydroxychloroquine has been politicized by Dr. Fauci and his 'deep state' partners as part of their Hybrid War on Trump's America.").

hydroxychloroquine for COVID-19.[55] Indeed, some of those being investigated for storming the U.S. Capitol on January 6, 2021 are prominent advocates for hydroxychloroquine.[56] This transformation into a political cause is most clearly evidenced by a lawsuit brought against Congressman Adam Schiff alleging that his letter to Facebook urging it to stop the spread of false medical information violates the First Amendment rights of those who would therefore be deprived of information.[57]

The vacuum created by the lack of any proven effective treatments for COVID-19 has created an almost unprecedented opportunity for pharmaceutical companies to expand the sale of their existing products. There are no legal barriers to physicians who wish to experiment by prescribing drugs for unapproved purposes. But the legal barriers that prevent pharmaceutical companies from promoting off-label use has turned them into nothing more than highly interested bystanders.[58]

The barriers to promoting off-label use of prescription drugs to fight COVID-19 do not extend beyond those who benefit financially: the pharmaceutical companies. Without the constraint of legal prohibitions or concerns over maintaining a professional license, individuals who promote off-label use of drugs find themselves in the position of unpaid spokespeople. A holding, no matter how unlikely, that these freelance promoters have First Amendment rights that obligate social media platforms to carry their message should ring alarm bells as close to unbelievable good fortune.

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55. *See Rush and Trump Were Right About Hydroxychloroquine*, RUSH LIMBAUGH SHOW (Mar. 10, 2021), https://www.rushlimbaugh.com/daily/2021/03/10/rush-and-trump-were-right-about-hydroxychloroquine/ ("You know, regarding hydroxychloroquine, Trump was right about hydroxychloroquine, and I think the problem with it is, it's so cheap. And Big Pharma must own Biden (chuckles) and must own Fauci as well. We've been using it.").

56. Zack Budryk, *Doctor that Promoted False Hydroxychloroquine Claims Arrested in Connection with Capitol Riot*, THE HILL (Jan. 21, 2021, 10:37 AM), https://thehill.com/policy/healthcare/535202-head-of-fringe-medical-group-who-met-with-pence-arrested-in-connection-with ("Federal officials this weekend arrested the head of a fringe medical group that has promoted false claims about vaccines and the antimalarial drug hydroxychloroquine in connection with the deadly Jan. 6 riot at the U.S. Capitol."); *see also* Amanda D'Ambrosio, *Simone Gold Arrested for Role in Capitol Insurrection*, MEDPAGETODAY (Jan. 20, 2021), https://www.medpagetoday.com/washington-watch/washington-watch/90778 ("Simone Gold, MD, JD, founder of the notorious pro-hydroxychloroquine, anti-vaccine group America's Frontline Doctors, was arrested Sunday for participating in storming the U.S. Capitol earlier this month[.]").

57. Complaint at 4, Ass'n of Am. Physicians & Surgeons v. Schiff, No. 1:20-cv-106, 2021 WL 354174 (D.D.C. Jan. 15, 2020), https://aapsonline.org/judicial/aaps-v-schiff-1-15-2020.pdf.

58. *See infra* Section III.

Amidst the sickness,[59] death,[60] and economic disaster[61] that the novel COVID-19 virus[62] has brought to the world had been the unprecedented spectacle of the President of the United States taking on the role of spokesman for two little used anti-malaria drugs,[63] hydrochloroquine,[64] marketed under the name Plaquenil,[65] and chloroquine (collectively referred to as hydroxychloroquine) that were, at the beginning of the pandemic, among the many medications being tried to combat a deadly new virus before there were any approved treatments or vaccines.[66] He did so against a background of a

59. *COVID Data Tracker*, CTRS. DISEASE CONTROL & PREVENTION, https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html (last accessed July 26, 2020).

60. The excess deaths count gives a more accurate death count attributable to COVID-19 at any point in time. *See Excess Deaths Associated with COVID-19*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm (last visited Jan. 23, 2021).

61. JOHNS HOPKINS UNIV., *COVID-19's Historic Economic Impact, in the U.S. and Abroad*, HUB at 2, 4 (Apr. 16, 2020), https://hub.jhu.edu/2020/04/16/coronavirus-impact-on-european-american-economies/.

62. *About COVID-19*, WASH. UNIV. IN ST. LOUIS, https://emergency.wustl.edu/coronavirus-disease-covid-19/covid-19-faqs/about-covid-19/#:~:text=COVID%2D19%20is%20a,to%20more%20serious%20diseases (accessed May 28, 2020).

63. Some of the mosquitos which carry Malaria have become resistant to its active ingredient chloroquine. *See Drug Resistance in the Malaria-Endemic World*, CTRS. FOR DISEASE CONTROL & PREVENTION, (July 23, 2018), https://www.cdc.gov/malaria/malaria_worldwide/reduction/drug_resistance.html.

64. Although the President frequently capitalizes it, "hydroxychloroquine sulfate" is actually the generic name for the drug manufactured by Sanofi as Plaquenil. *See* SANOFI-AVENTIS CANADA INC., *Product Monograph Including Patient Medication Information*, at 4, 24 (Oct. 18, 2021), http://products.sanofi.ca/en/plaquenil.pdf ("PLAQUENIL (hydroxychloroquine sulfate tablets) belongs to the 4-aminoquinoline class. PLAQUENIL has been beneficial for patients with rheumatoid arthritis and lupus erythematosus, especially chronic discoid lupus. The exact mode of action in controlling these diseases is unknown. The action of this compound against malarial parasites is similar to that of chloroquine phosphate."); *see* ASHP, *Hydroxychloroquine*, DRUGS.COM (Nov. 29, 2021), https://www.drugs.com/hydroxychloroquine.html ("Hydroxychloroquine is a quinoline medicine used to treat or prevent malaria, a disease caused by parasites that enter the body through the bite of a mosquito. Malaria is common in areas such as Africa, South America, and Southern Asia. This medicine is not effective against all strains of malaria. Hydroxychloroquine is not effective against all strains of malaria, or against malaria in areas where the infection has been resistant to a similar drug called chloroquine. Hydroxychloroquine is also used to treat symptoms of rheumatoid arthritis and discoid or systemic lupus erythematosus.").

65. *See* SANOFI-AVENTIS CANADA INC., *Product Monograph Including Patient Medication Information*, at 4 (Oct. 18, 2021), http://products.sanofi.ca/en/plaquenil.pdf.

66. *See* Joseph M. Geskey, *Off-Label Prescribing in the Era of COVID-19*, MED. ECON. at 1 (Apr. 14, 2020), https://www.medicaleconomics.com/view/label-prescribing-era-covid-19 ("Despite no evidence-based literature supporting a standard-of-care for coronavirus infections, many providers are prophylactically prescribing medications like Hydroxychloroquine and Azithromycin in the hope that it will arrest the virus from causing a 'cytokine storm.'"); *see also* Steve Almond, *Why America Can't Stop COVID-19*, WBUR (May 13, 2020), https://www.wbur.org/cognoscenti/2020/05/13/coronavirus-donald-trump-gop-steve-almond. The

global pandemic where every country was facing ever increasing numbers of cases, hospitalizations, and deaths in an environment without the existence of a single treatment option approved by any national regulatory or creditable scientific entity. In the absence of anything that could prevent the disease or mitigate its severity, doctors used drugs approved for other purposes or populations that they hoped would interfere with the virus' replication or at least reduce the severity of its life-threatening symptoms. The search for effective therapeutic treatments advanced in parallel with intense efforts to develop vaccines.[67] By December 2021, there were three FDA approved vaccines to prevent COVID-19.[68] That some month, the FDA issued an emergency use authorization for Pfizer's Paxlovid.[69] Biomedical researchers are still developing specific treatments.[70] Many initially promising interventions, like convalescent plasma, have been reluctantly abandoned because they make no difference in death rates or disease progression.[71]

We may never know the exact reason for the President's relentless advocacy, which continued long after the FDA withdrew its EUA.[72] It continued despite

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FDA approved the first treatment for Covid-19, eklury (remdesivir), on October 22, 2020. *FDA Approves First Treatment for COVID-19*, U.S. FOOD & DRUG ADMIN. (Oct. 22, 2020), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19. The first vaccine received FDA approval on August 23, 2021. *FDA Approves First COVID-19 Vaccine*, U.S. FOOD & DRUG ADMIN. (Aug. 31, 2021), https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine.

67. *COVID-19 therapeutics: Challenges and directions for the future*, PNAS, https://www.pnas.org/doi/10.1073/pnas.2119893119 (last visited Apr. 8, 2022).

68. Office of the Commissioner, *COVID-19 Vaccines*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines (last visited Apr. 8, 2022).

69. Office of the Commissioner, *Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19* (2021), U.S. FOOD & DRUG ADMIN., https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19 (last visited Apr. 8, 2022).

70. *COVID-19 therapeutics: Challenges and directions for the future*, *supra* note 67; Christopher Curley, *Fluvoxamine Effective as a COVID-19 Treatment*, HEALTHLINE (2022), https://www.healthline.com/health-news/fluvoxamine-found-to-be-effective-as-a-covid-19-treatment-the-benefits-and-limitations (last visited Apr. 8, 2022).

71. Rita Rubin, *Once Viewed as a Promising COVID-19 Treatment, Convalescent Plasma Falls.* Maia Anderson, *3 drugs that have failed to benefit COVID-19 patients in clinical trials*, BECKER'S HOSPITAL REVIEWS (Nov. 18, 2020), https://www.beckershospitalreview.com/pharmacy/3-drugs-that-have-failed-to-benefit-covid-19-patients-in-clinical-trials.html. *See also Out of Favor*, JAMA (Mar. 9, 2022), https://jamanetwork.com/journals/jama/fullarticle/2790074.

72. The FDA issued its EUA for hydroxychloroquine on March 20, 2020 and withdrew it on June 15, 2020. *See* Elangovan Manivannan et al., *The Rise and Fall of Chloroquine/ Hydroxychloroquine as Compassionate Therapy of COVID-19*, 12 FRONT. PHARMACOL. 584940 (2021). Facher et al., *supra* note 34. *See also* Andre C. Kalil, *Treating COVID-19–Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics*, 323 J. AM. MED. ASS'N 1897–98 (2020).

being contradicted directly by his chief science advisor, Dr. Anthony Fauci.[73] The President himself frequently denied any personal financial interest in launching what had become an orphan drug with few uses. Malarial mosquitos have long been immune to its effects, but it was certainly of financial interest to the companies authorized to sell it. Whatever his motive, the success of President Trump's advocacy for hydroxychloroquine became visible almost immediately.

D. The Case of Ivermectin

While President Trump was advocating for the use hydroxychloroquine, many of the same medical entities promoting that drug were also enthusiastic about the off-label repurposing of another FDA approved drug, ivermectin.[74] One of the first mainstream media mentions of ivermectin came from testimony in front of the U.S. Senate Homeland Security Committee in testimony from Dr. Pierre Kory.[75] Dr. Kory, a pulmonologist from Wisconsin, was "president of the Front Line COVID-19 Critical Care Alliance (FLCCC), a group of physicians and scientists who champion ivermectin, along with other drugs and vitamins with dubious efficacy against COVID."[76] Since then, there has been a consistent stream of reporting about the FLCCC as well as the British Ivermectin Recommendation Development (BIRD) Group and America's Frontline Doctors (AFLDS) advocating for ivermectin's use to prevent and treat COVID-19.[77]

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73. Justin Baragona, *Dr. Fauci Rails Against COVID Disinformation Video Featuring Demon Sperm Doctor*, DAILY BEAST (July 29, 2020, 2:53 PM), https://www.thedailybeast.com/dr-fauci-rails-against-covid-disinformation-video-featuring-demon-sperm-doctor.

74. Emma Goldberg, *Demand Surges for Deworming Drug for Covid, Despite Scant Evidence It Works*, N.Y. TIMES (Aug. 30, 2021), https://www.nytimes.com/2021/08/30/health/covid-ivermectin-prescriptions.html; Carl Zimmer, *Ivermectin Does Not Reduce Risk of Covid Hospitalization, Large Study Finds*, N.Y. TIMES (Mar. 30, 2022), https://www.nytimes.com/2022/03/30/health/covid-ivermectin-hospitalization.html?searchResultPosition=1; Christina Szalinski, *Fringe Doctors' Groups Promote Ivermectin for COVID despite a Lack of Evidence*, SCI. AM. (Sept. 29, 2021), https://www.scientificamerican.com/article/fringe-doctors-groups-promote-ivermectin-for-covid-despite-a-lack-of-evidence/.

75. Oscar Gonzalez, *Ivermectin: Why Are There Lawsuits Over This Unproven Drug*, CNET (Oct. 6, 2021, 5:00 AM), https://www.cnet.com/health/medical/ivermectin-and-covid-19-why-are-there-lawsuit-over-this-unproven-drug/; Christina Szalinski, *Fringe Doctors' Groups Promote Ivermectin for COVID despite a Lack of Evidence*, SCI. AM. (Sept. 29, 2021), https://www.scientificamerican.com/article/fringe-doctors-groups-promote-ivermectin-for-covid-despite-a-lack-of-evidence/#.

76. Christina Szalinski, *Fringe Doctors' Groups Promote Ivermectin for COVID despite a Lack of Evidence*, SCI. AM. (Sept. 29, 2021), https://www.scientificamerican.com/article/fringe-doctors-groups-promote-ivermectin-for-covid-despite-a-lack-of-evidence/#.

77. BRITISH IVERMECTIN RECOMMENDATION DEVELOPMENT, https://bird-group.org/; AMERICA'S FRONTLINE DOCTORS, https://americasfrontlinedoctors.org/. *See* Nick Robins-Early, *Ivermectin Frenzy: the Advocates, Anti-vaxxers and Telehealth Companies Driving Demand*, THE GUARDIAN (Sept. 13, 2021, 6:00 AM), https://www.theguardian.com/world/2021/sep/13/ivermectin-treatment-covid-19-anti-vaxxers-advocates (describing the two organizations as being part of "a cottage industry of advocacy groups, anti-vaccine activists and telehealth companies").

The consensus of the scientific community in the United States and abroad is that ivermectin is not effective in either treating or preventing COVID.[78] The FDA has publicly and aggressively advocated against the use of ivermectin to treat COVID-19, writing that "[t]here's a lot of misinformation around, and you may have heard that it's okay to take large doses of ivermectin. It is not okay."[79] On August 26, 2021, the CDC released an emergency warning stating that, "[d]uring the COVID-19 pandemic, ivermectin dispensing by retail pharmacies has increased, as has use of veterinary formulations available over the counter but not intended for human use."[80] Citing a study that there had been a "a 24-fold increase" of ivermectin prescriptions "from the pre-pandemic baseline," the warning linked this increase to "a three-fold increase in the number of calls for human exposures to ivermectin in January 2021" made to poison control centers across the United States.[81] In July 2021, calls to poison control centers about ivermectin increased five-fold from baseline.[82] In response, the FDA issued a warning that:

> Even the levels of Ivermectin for approved human uses can interact with other medications, like blood-thinners. You can also overdose on Ivermectin, which can cause nausea, vomiting, diarrhea, hypotension (low blood pressure), allergic reactions (itching and hives), dizziness, ataxia (problems with balance), seizures, coma and even death.[83]

Other organizations issuing similar warnings include the American Pharmacists Association, American Medical Association, Cleveland Clinic, and Mayo Clinic.[84]

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78. *EMA Advises Against Ivermectin Use for Covid-19 Outside Clinical Trials*, PHARM. TECH. (Mar. 23, 2021), https://www.pharmaceutical-technology.com/news/ivermectin-anti-parasite-use-covid-19/ ("EMA concluded that the currently available evidence is not enough to support the ivermectin's use for COVID-19 outside clinical trials."); *Ivermectin is a Nobel Prize-Winning Wonder Drug – but Not for COVID-19*, THE CONVERSATION (Oct. 14, 2021, 8:15 AM), http://theconversation.com/ivermectin-is-a-nobel-prize-winning-wonder-drug-but-not-for-covid-19-168449.

79. *Why You Should Not Use Ivermectin to Treat or Prevent COVID-10*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19 (last accessed Feb. 16, 2022).

80. *Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19*, CTRS. FOR DISEASE CONTROL & PREVENTION: HEALTH ALERT NETWORK (Aug. 26, 2021, 11:40 AM), https://emergency.cdc.gov/han/2021/han00449.asp.

81. *Id.*

82. *Id.*

83. *Why You Should Not Use Ivermectin to Treat or Prevent COVID-19*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19 (last accessed Feb. 16, 2022).

84. Sara Berg, *Why Ivermectin Should Not Be Used to Prevent or Treat COVID-19*, AM. MED. ASS'N (Sept. 2, 2021), https://www.ama-assn.org/delivering-care/public-health/why-ivermectin-should-not-be-used-prevent-or-treat-covid-19; *Why You Shouldn't Take Ivermectin for COVID-19*,

Ivermectin has long been associated with serious neurological side-effects in some people when taken as an anti-parasitic.[85] While the reason some people suffered from these side-effects while others did not is still the subject of scientific review, the idea of people who were not infected with parasites or who were taking it at the larger doses prescribe for animals caused immediate concern in the scientific community most familiar with its use. This included not just the major global health regulators and national health authorities, but also the drug's own manufacturer, Merck.[86]

As use of ivermectin became more common, state health departments began putting out statements, such as this one from Alabama, warning that "[t]he agency has received multiple reports of patients who have required medical support and have been hospitalized after taking high doses of ivermectin which can be highly toxic in humans. Side effects occur, and drug interactions are common."[87] Similar warnings have been issued by health departments in South Carolina.[88] Yet despite continued evidence that ivermectin is not effective in

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CLEVELAND CLINIC (Aug. 30, 2021), https://health.clevelandclinic.org/why-you-shouldnt-take-animal-ivermectin-for-covid-19/; Daniel C. DeSimone, M.D., *COVID-19 drugs: Are there any that work?*, MAYO CLINIC (Feb. 19, 2022), https://www.mayoclinic.org/diseases-conditions/coronavirus/expert-answers/coronavirus-drugs/faq-20485627.

85. Rebecca E. Chandler, *Serious Neurological Adverse Events After Ivermectin—Do They Occur Beyond the Indication of Onchocerciasis?*, 98 AM. J. TROP. MED. HYG. 382–88 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5929173/ ("Examples of serious neurological adverse events reported included such terms as unable to walk, consciousness disturbed or depressed level of consciousness or loss of consciousness, seizure or convulsion, encephalopathy or coma, and tremor."); *see also* Duong Khanh Toan et al., *Ivermectin Poisoning – Report of Successful Management*, 58 INDIAN PEDIATRICS 893 (2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8464184/pdf/13312_2021_Article_2316.pdf ("[S]eizures may be the clinical presentation in children with cardiac channelopathy. Red flags such as a family history of sudden death, seizures associated with auditory triggers and recurrent seizures with a normal EEG should raise suspicion and prompt referral to a pediatric cardiologist.").

86. *See, e.g.*, Nial Wheate, Andrew McLachlan & Slade Matthews, *Thinking of Trying Ivermectin for COVID? Here's What Can Happen With This Controversial Drug*, UNIV. OF SYDNEY (Sept. 3, 2021), https://www.sydney.edu.au/news-opinion/news/2021/09/03/-thinking-of-trying-ivermectin-for-covid-heres-what-can-happen-w.html; *see also Risks of Importing or Prescribing Ivermectin for Prevention or Treatment of COVID-19*, N.Z. MEDS. & MED. DEVICES SAFETY AUTH. (Sept. 6, 2021), https://www.medsafe.govt.nz/safety/Alerts/ivermectin-covid19.htm; *Merck Statement on Ivermectin Use During the COVID-19 Pandemic*, MERCK (Feb. 4, 2021, 11:45 AM), https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/.

87. *ADPH Warns About Dangers of Self-Medicating With Large Quantities of Ivermectin*, WBRC (Aug. 25, 2021, 4:32 PM), https://www.wbrc.com/2021/08/25/adph-warns-about-dangers-self-medicating-with-large-quantities-ivermectin/.

88. *See The Dangers of Using Hydroxychloroquine and Ivermectin for Preventing or Treating COVID-19*, S.C. DEP'T OF HEALTH AND ENV'T CONTROL, https://scdhec.gov/covid19/dangers-using-hydroxychloroquine-ivermectin-preventing-or-treating-covid-19 ("Do not swallow ivermectin lotion or cream that is meant for use on the skin. Taking large doses or doses intended for animals is dangerous and can result in overdose, causing serious harm including nausea, vomiting, diarrhea, low blood pressure, dizziness, balance problems, seizures, coma, and even death. Ivermectin can cause birth defects if taken early in pregnancy. Dosages intended for animals

treating or preventing COVID, its use remains popular.[89] Many states have passed or are considering legislation to make it easier for residents to obtain ivermectin.[90] While it is impossible to know if this misplaced faith in ivermectin as with hydroxychloroquine has prevented people from seeking effective treatments or vaccines, there is considerable evidence that those predisposed to be skeptical of vaccines were often strong advocates of both drugs.[91]

II. OUTLINING THE LEGAL FRAMEWORK OF OFF-LABEL PRESCRIBING

A. Constitutional Basis of the Federal and State Shared Regulation of Prescription Drugs

The current scheme of federal regulation over drugs is based on a 1906 law[92] that exercised the power granted to Congress under the Commerce Clause of the U.S. Constitution to preempt the power states usually have over matters of health and safety and "prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs."[93] This initial dual mission of protecting consumers from false claims and unsafe products began a process that continues into the present of Congress asserting more and more federal control over the manufacturing and distribution of what it defines as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals."[94]

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may contain ingredients that are not meant for people to consume, and how these ingredients can affect humans has not been studied.").

89. Leana Wen, The Checkup With Dr. Wen: Ivermectin (still) does not work against covid-19, WASH. POST, https://s2.washingtonpost.com/camp-rw/?trackId=5a5b6ed1ade4e246b1fcd250&s=624f4c6764253a7f3421612f&linknum=5&linktot=61 (last visited Apr. 8, 2022); Jennifer Reich, *Why vaccine skeptics are all in on ivermectin*, WASH. POST (Sept. 7, 2021), https://www.washingtonpost.com/outlook/2021/09/07/ivermectin-vaccine-skeptics/; Steven Chee Loon Lim et al., *Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial*, 182 JAMA INTERN. MED. 426–35 (2022).

90. WCYB, *Tennessee Senate passes bill to allow ivermectin to be bought for COVID-19 treatment*, ABC 13 NEWS (Apr. 6, 2022), https://wset.com/news/coronavirus/tn-senate-passes-legislation-to-allow-ivermectin-to-be-purchased-over-the-counter; Adrianna Rodriguez, *Lawmakers push legislation to protect doctors who prescribe ivermectin for COVID-19. Can they do that?*, USA TODAY (Mar. 10, 2022), https://www.usatoday.com/story/news/health/2022/03/10/covid-ivermectin-bill-dozens-states-push-laws-protect-doctors/9356967002/.

91. Jennifer Reich, *Why vaccine skeptics are all in on ivermectin*, WASH. POST (Sept. 7, 2021), https://www.washingtonpost.com/outlook/2021/09/07/ivermectin-vaccine-skeptics/.

92. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq.

93. *Milestones in U.S. Food and Drug Law*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law (last updated Jan. 31, 2018).

94. 21 U.S.C. 321(g)(1)(B); *see also Definition of a Drug (April 2017)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/fda-drug-info-rounds-video/definition-drug-april-2017 (last updated Apr. 26, 2017).

1. Federal Regulation of the Sale and Use of Prescription Drugs

Off-label prescribing is possible because, while the federal government has preempted some of the states' inherent power recognized by the 10th Amendment to regulate matters of health and safety by vesting the FDA with power to approve drugs, it has left states with the power to regulate the providers who prescribe the drugs the FDA approves.[95]

Under the current system of regulation, the FDA has the authority to require drug manufactures to "demonstrate, through clinical trials, the safety and efficacy of a new drug for each intended use or indication."[96] Once this is proved to the FDA's satisfaction, it has the authority to make two decisions: first, whether the drug should be available only through a prescription;[97] and second, what information must be included with the drug to provide doctors and patients sufficient information to understand the terms of its approval.[98] With the power transferred from the FDA to the states comes the authority to prescribe an FDA "approved drug" for "an unapproved use."[99]

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95. *See* Gibbons v. Ogden, 22 U.S. 1, 203 (1824) (describing state police power as an "immense mass of legislation, which embraces every thing within the territory of a state, not surrendered to the general government [including] [i]nspection laws, quarantine laws, health laws of every description"); Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 321(g)(1)(B) (The FFDCA defines "drugs" as "articles" whose manufacturers claim are "intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease."); Nadia N. Sawicki, *Character, Competence, and the Principles of Medical Discipline*, 13 J. HEALTH CARE L. & POL'Y 285, 289–94 (2010) (citing Dent v. West Virginia, 129 U.S. 114, 122 (1889)) (tracing state authority to establish medical licensing boards through its history and practice); *Human Drugs*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/industry/regulated-products/human-drugs (last updated on Mar. 5, 2021); *see also* Jacobson v. Massachusetts, 197 U.S. 11, 25 (1905); U.S. Const. amend. X ("The powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively, or to the people."); Elizabeth Weeks Leonard, *State Constitutionalism and the Right to Health Care*, 12 U. PA. J. CONST. L. 1325, 1329–30 (2010) ("By contrast to several state constitutions, the federal constitution does not expressly reference the word 'health' in any provision."). Donald D. Ashley, *Clarifying Misconceptions About US Food and Drug Administration Unapproved Drugs Program*, 127 ANESTHESIA & ANALGESIA 1292, 1292 (2018) ("Drug regulation was first brought under federal law in 1906 with passage of the original Federal Food and Drug Act, which prohibited the sale of adulterated and misbranded drugs, but did not require drugs be preapproved by the FDA."); Mut. Pharm. Co. v. Bartlett, 570 U.S. 472, 486–87 (2013) (the FDCA preempts state law when it is impossible for drug manufacturers to comply with the laws of different states simultaneously).

96. United States v. Caronia, 703 F.3d 149, 153 (2d Cir. 2012) (citing 21 U.S.C. § 355(d)); *see* Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 612–14, (1973).

97. United States v. Caronia, 703 F.3d 149, 152–53 (2d Cir. 2012) (citing 21 U.S.C. § 355(a)) ("The FDCA [requires that] before drugs are distributed into interstate commerce, they must be approved by the FDA for specific uses.").

98. *See id.* at 154; *see also* Lars Noah, *Constraints on the Off-Label Uses of Prescription Drug Products*, 16 J. PRODS. & TOXICS LAB 139, 141 (1994) (off label prescribing can also involve using a different method of delivering the drug to the patient than was approved in the original approval process such as a drug approved for oral use being given intravenously).

99. *See Understanding Unapproved Use of Approved Drugs "Off Label,"* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options

Over time, the FDA's mandate expanded beyond assuring safety so that today it has the legal authority to determine whether the drugs, biologics, and vaccines it regulates are also effective for their approved "specific uses."[100] The FDA also has the authority to designate whether a drug "requires a doctor's authorization to purchase."[101] If the FDA concludes that the evidence provided by the entity seeking approval of the drug—the "sponsor" or "manufacturer"—is adequate, then the last step is for the FDA to announce the conditions under which it can be sold to the public. These conditions of use are referred to as the "label" even though they are printed on separate sheets of paper, not actually attached to the bottle The label includes the FDA's decision about whether the drug can be made available through direct purchase by a consumer or through the order of a licensed prescriber.[102] The end of this labeling process marks the end of the FDA's oversight and the beginning of state control.[103]

/understanding-unapproved-use-approved-drugs-label (last updated Feb. 5, 2018); *see also Off-Label Drugs: What You Need to Know*, AGENCY FOR HEALTHCARE RSCH. & QUALITY, https://www.ahrq.gov/patients-consumers/patient-involvement/off-label-drug-usage.html (last updated Sept. 2015) ("Off-label prescribing is when a physician gives you a drug that the U.S. Food and Drug Administration (FDA) has approved to treat a condition different than your condition. This practice is legal and common. In fact, one in five prescriptions written today are for off-label use.").

100. Janet Woodcock, M.D., *Safety, Efficacy, and Quality Remain Top Priorities as We Continue Our Work to Expand Access to Cost-Saving Generic Drugs for the American Public*, U.S. FOOD & DRUG ADMIN. (May 13. 2019), https://www.fda.gov/news-events/fda-voices/safety-efficacy-and-quality-remain-top-priorities-we-continue-our-work-expand-access-cost-saving.

101. *See Drugs@FDA Glossary of Terms*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#P (choose letter "P" from glossary selection; then scroll to the definition for "Prescription Drug Product") (last updated Nov. 14, 2017).

102. *See* 21 U.S.C. § 353(b)(1) ("A drug intended for use by man which because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug.").

103. *See* 21 U.S.C. § 355-1(f)(1) (The FDA has limited authority to restrict the terms under which providers can prescribe drugs by making "Elements to Assure Safe Use" as part of the label. It also has limited authority to initiate an action to withdraw approval if there is substantial evidence that the drug is harmful in ways not revealed during testing); *see also Understanding Licensing, Credentialing, Certification, and Privileging*, ASS'N OF STATE AND TERRITORIAL HEALTH OFFS., https://astho.org/Programs/Preparedness/Public-Health-Emergency-Law/Scope-of-Practice-Toolkit/Understanding-Licensing,-Credentialing,-Certification,-and-Privileging(2) (last visited Aug. 2, 2020); *see also* Jennifer S. Bard, *Putting Patients First: How the FDA Could Use Its Existing Powers to Reduce Post-Market Adverse Events*, 10 IND. HEALTH L. REV. 495, 516–17 (2013) ("Once the FDA approves a drug or device is then that it becomes available for any physician to prescribe to any patient.").

2. State Regulation of Prescribing Authority

Congress has been explicit that the FDA's authority extends only to the regulation of drugs, not to the regulation of the practice of medicine.[104] States retain their power over the use of prescription drugs so long as they do not 1) act in a way that undermines the federal government's authority under the FDA;[105] and 2) obey the additional restrictions that Congress has placed on prescribing drugs that have been designated as especially dangerous and subject to criminal diversion.[106] Other than these two provisions, states can decide both who can prescribe drugs,[107] and the criteria for doing so.[108] The restrictions that do exist under state law involve additional procedures for drugs that are likely to be abused.[109] Today, all states extend full prescribing power beyond M.D.s, to include osteopaths, dentists, veterinarians (for animals), and nurse

104. *See* 21 U.S.C. § 396 ("Nothing in this chapter shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship."); *see also* George Horvath, *Off-Label Drug Risks: Toward a New FDA Regulatory Approach*, 29 ANNALS HEALTH L. 101, 116 (2020) ("In general, the Agency has eschewed attempts at directly prohibiting physicians from prescribing drugs for off-label indications."); *see generally* Jeffrey K. Aronson & Robin E. Ferner, *Unlicensed and Off-Label Uses of Medicines: Definitions and Clarification of Terminology*, 83 BRITISH J. CLINICAL PHARMACOLOGY 2615, 2616, 2618 (2017) (In contrast, in the United Kingdom the same entity licenses physicians and oversees drug approval allowing for a more coordinated approach).

105. *See generally* Elizabeth Y. McCuskey, *Body of Preemption: Health Law Traditions and the Presumption of Against Preemption*, 89 TEMP L. REV. 95, 114–117 (2016) (tracing development of application of health regulation activities to the Police Power).

106. Mut. Pharm. Co. v. Bartlett, 570 U.S. 472, 495–96 (2013) (the FFDCA preempts state law when it is impossible for drug manufacturers to comply with the laws of different states simultaneously).

107. This is an on-going process and the laws in any particular state are likely to be different at any specific time. *See State Law Fact Sheet: A Summary of Nurse Practitioner Scope of Practice Laws, in Effect April 2016*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/dhdsp/pubs/docs/SLFS_NSOP_508.pdf (last accessed Feb. 18, 2022); *see also State Practice Environment*, AM. ASSOC. OF NURSE PRACTITIONERS, https://www.aanp.org/advocacy/state/state-practice-environment (last accessed July 29, 2020); *see, e.g.*, *Who Can Prescribe and Administer Prescriptions in Washington State*, WASH. STATE DEP'T OF HEALTH, https://www.doh.wa.gov/LicensesPermitsandCertificates/ProfessionsNewReneworUpdate/PharmacyCommission/WhoCanPrescribeandAdministerPrescriptions (last accessed July 29, 2020).

108. Every state has laws intended to reduce opioid deaths by limiting the prescription of opioids. For an overview of state laws, *see Prescription Drug Time and Dosage Limit Laws*, CTRS. FOR DISEASE CONTROL & PREVENTION, (Mar. 5, 2015), https://www.cdc.gov/phlp/docs/menu_prescriptionlimits.pdf; Marilyn Bulloch, *Opioid Prescribing Limits Across the States*, PHARM. TIMES (Feb. 5, 2019), https://www.pharmacytimes.com/contributor/marilyn-bulloch-pharmd-bcps/2019/02/opioid-prescribing-limits-across-the-states.

109. *See, e.g.*, N.J. ADMIN. CODE § 13:35-7.8(a) (2022) ("A practitioner shall not prescribe, order, dispense, administer, sell or transfer any amphetamine or sympathomimetic amine designated as a Schedule II controlled substance for use in weight management, dieting or any other anorectic purpose, or for the treatment of fatigue.").

practitioners.[110] In addition, many states have extended limited, Second Tier prescribing privileges to physician's assistants, Certified Registered Nurse Anesthetists, Naturopathic Doctors, Optometrists, psychologists, and Pharmacists.[111]

B. How Common is Off-Label Prescribing?

By some estimates, as many as one in five prescriptions in the United States are "written 'off-label.'"[112] While there is wide agreement that prescribing drugs off-label is a longstanding and deeply embedded part of clinical practice in the United States, exactly how much and by whom is hard to determine. There is no generally accepted number of annual off-label prescriptions. By some estimates as many as 30% of all prescriptions are off-label and in fields like oncology, the number is likely much higher.[113] The most commonly reported areas for off-label prescribing are in oncology, dermatology,[114] palliative

110. For a history of the development of the profession of nurse practitioners, *see* John Michael O'Brien, *How Nurse Practitioners Obtained Provider Status: Lessons for Pharmacists*, 60 AM. J. HEALTH SYS. PHARM. 2310 (2003), https://www.medscape.com/viewarticle/464663_2; For a 50 state survey of the extent to which Nurse Practitioners have prescriptive authority, *see State Law Chart: Nurse Practitioner Prescriptive Authority*, AM. MED. ASS'N, https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/specialty%20group/arc/ama-chart-np-prescriptive-authority.pdf (last visited Feb. 18, 2022).

111. *Prescriptive Authority*, MED. DICTIONARY (2009), https://medical-dictionary.thefreedictionary.com/prescriptive+authority; *State Approaches to Scope of Practice: Certified Registered Nurse Anesthetists*, ARK. CTR. FOR HEALTH IMPROVEMENT, https://achi.net/library/scope-of-practice-nurse-anesthetist/ (accessed Aug. 2, 2020); *Do Naturopathic Doctors Prescribe Medication?*, INST. FOR NAT. MED., https://naturemed.org/faq/do-naturopathic-doctors-prescribe-medication (last accessed Aug. 2, 2020); *Winter 2007/Spring 2008 Newsletter, Drugs That May be Prescribed by Optometrists*, TEX. STATE BD. OF PHARMACY, https://www.pharmacy.texas.gov/files_pdf/Optometrists.pdf (last accessed Aug. 2, 2020), http://web.archive.org/web/20200304113303/https://www.pharmacy.texas.gov/files_pdf/Optometrists.pdf; David J. Reinhardt, *Psychologist's Prescribing: A Threat or a Promise*, MEDSCAPE (June 24, 2010) https://www.medscape.com/viewarticle/723997_2; Gloria Sachdev et al., *Current Status of Prescriptive Authority by Pharmacists in the United States*, 3 J. AM. COLL. OF CLINICAL PHARMACY 807 (2020).

112. Carah Wertheimer, *1-in-5 Prescriptions Are Off-Label: What You Don't Know Could Hurt You*, MEDTRUTH.COM (Mar. 17, 2020), https://medtruth.com/articles/health-features/off-label-prescriptions/; *Off-Label Drugs: What You Need to Know*, AGENCY FOR HEALTHCARE RSCH. & QUALITY, https://www.ahrq.gov/patients-consumers/patient-involvement/off-label-drug-usage.html (last accessed July 26, 2020).

113. Shariful A. Syed, Brigham A. Dixson, Eduardo Constantino & Judith Regan, *The Law and Practice of Off-Label Prescribing and Physician Promotion*, 50 J. AM. ACAD. PSYCHIATRY & L. 1, 2 (2021), http://jaapl.org/content/early/2020/11/24/JAAPL.200049-20 ("In recent studies in community clinical practices, 40 to 80 percent of recipients of commonly prescribed psychotropic medications (including antidepressants, antipsychotics, and anticonvulsants) were receiving these medications for off-label indications")(*citing* J. Wong, A. Motulsky & M. Abrahamowicz, *Off-Label Indications For Antidepressants In Primary Care: Descriptive Study Of Prescriptions From An Indication Based Electronic Prescribing System*, 356 BMJ 603 (2017).

114. Katelin França & Sergio Litewka, *Controversies in Off-label Prescriptions in Dermatology: The Perspective of the Patient, the Physician, and the Pharmaceutical Companies*,

medicine,[115] and psychiatry.[116] One specialty that was, until recently, almost completely dependent on off-label drugs was pediatrics. In a report accompanying amendments to the Federal Food, Drug, and Cosmetics Act, Senator Jim Jeffords wrote, "[c]hildren have for years been wrongly considered 'small adults' when estimating the effect of prescription drugs on their overall health. Currently there is no systematic means for testing the safety and efficacy of drugs on the pediatric population."[117]

Because there is nothing illegal about off-label prescribing, there are no requirements to monitor it. Some estimates of which drugs are most commonly prescribed for which conditions have come from analyzing the Medicare prescribing records,[118] but currently most estimates are based on surveys of prescribers themselves.[119] But while there is no precise information about how many patients receive drugs off-label, there is strong and consistent evidence that doctors believe that off-label prescribing is an essential part of practicing medicine.[120] Oncologists, by some estimates prescribe as much as eighty percent of medications off label, contend that developments move so quickly, and their patients are so sick that they cannot wait for final approval.[121]

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58 INT'L J. DERMATOLOGY 788, 789 (2019) ("It is estimated that 21% of the prescriptions in the United States are off-label . . . Off-label prescribing involved an unapproved indication in 56.4% of cases, a lower dosage (26.5%) or higher dosage (19.5%) than specified, age not labeled (7.2%), incorrect route of administration (3.5%), and contraindication (0.3%)").

115. Vera Hagemann et al., *Drug Use Beyond the License in Palliative Care: A Systematic Review and Narrative Synthesis*, 33 PALLIATIVE MED. 650, 655 (2019).

116. Aishwarya Vijay et al., *Patterns and Predictors of Off-Label Prescription of Psychiatric Drugs*, 13 PLOS ONE 1, 2 (2018) ("This practice is legal and common—a 2003 report showed that for the 3 leading drugs in each of the 15 leading drug classes, off-label use accounted for approximately 21% of prescriptions.").

117. S. REP. NO. 105-43, at 3 (1997).

118. Christopher C. Yang & Mengnan Zhao, *Determining Associations with Word Embedding in Heterogeneous Network for Detecting Off-Label Drug Uses*, IEEE COMPUTER SOCIETY (2017), http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=8031200&isnumber=8031114.

119. Christopher C. Yang & Mengnan Zhao, *Determining Associations with Word Embedding in Heterogeneous Network for Detecting Off-Label Drug Uses*, IEEE COMPUTER SOCIETY (2017), http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=8031200&isnumber=8031114.
W. David Bradford et al., *Off-Label Use of Pharmaceuticals: A Detection Controlled Estimation Approach*, 66 J. INDUS. ECON. 866 (2018); Aviv Ladanie et al., *Off-label Treatments Were Not Consistently Better or Worse than Approved Drug Treatments in Randomized Trials*, 94 J. CLINICAL EPIDEMIOLOGY 35 (2018).

120. George Horvath, *Off-Label Drug Risks: Toward a New FDA Regulatory Approach*, 29 ANNALS HEALTH L. 101, 110–11 (2020) ("Data reported in 2003 indicated that, overall, twenty-two percent of all prescriptions were for off-label indications. In some patient groups, this number may exceed seventy percent.").

121. *See generally* I. Glenn Cohen, *Therapeutic Orphans, Pediatric Victims? The Best Pharmaceuticals for Children Act and Existing Pediatric Human Subject Protection*, 58 FOOD & DRUG L.J. 661, 661 (2003) (describing the development of regulations encouraging increased research on pediatric drug safety and expressing concerns that it would have the consequence of putting more children at risk as research subjects). *See also Off-label Drug Use*, AM. CANCER

C. Safety Concerns Regarding Off-Label Prescribing

A recent report to Congress on its options for regulating off-label prescribing listed ten different "[p]ossible [a]venues of [f]uture [c]ongressional [i]nterest" based on concerns that the current system risked the safety of patients because it evades current laws requiring that drugs be proved safe and effective by the FDA.[122] Regulators, patient advocates, and physicians themselves express concerns about off-label prescribing as it exposes patients to risks from drugs,[123] which have not been found by the FDA to be safe and efficacious for them.[124] Speaking in the context of widespread publicity about the harm caused by off-label prescription of two FDA approved medications for weight loss, bioethicists Rebecca Dresser and Joel Frader warned that "[o]ff-label prescribing can expose patients to risky and ineffective treatments."[125] A recent Congressional Research Service (CRS) report notes that after the first reports of success with using intravenous ketamine for the treatment of depression and migraines, physicians were able to set up commercial clinics even though the FDA had not yet "reviewed clinical data that could support the clinics' promotional claims of safety and effectiveness."[126] By some estimates, less than half of the clinical trials approved by the FDA result in petitions for approval.[127] The FDA reports that between 2011 and 2018 it "approved 309 novel drugs, of which 261 (84%)

SOC'Y, https://www.cancer.org/treatment/ treatments-and-side-effects/treatment-types/off-label-drug-use.html (last accessed July 26, 2020).

122. *See* Susan Thaul, CONG. RSCH. SERV., R45792, OFF-LABEL USE OF PRESCRIPTION DRUGS 9–12 (2019).

123. *Id.* at 9, 14 ("Prescriptions for off-label uses of FDA-approved drugs are made without the benefit of an FDA-reviewed analysis of safety and effectiveness data.").

124. Tewodros Eguale et al., *Association of Off-label Drug Use and Adverse Drug Events in an Adult Population*, 176 J. AM. MED. ASS'N INTERNAL MED. 55, 55 (2015) (exploring the risks of off-label drug use in Canada).

125. Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 476–78 (2009) (describing physicians' discretion in prescribing drugs at dosages or using methods of administration not specified on the label).

126. Susan Thaul, CONG. RSCH. SERV., R45792, OFF-LABEL USE OF PRESCRIPTION DRUGS 1–3 (2019) ("In a 2006 study of drug prescribing by office-based physicians, 21% of prescriptions were written for off-label uses. Of those off-label prescriptions, the study's authors found that 27% were backed by strong scientific support. A 2016 Canadian study of primary care clinics found an overall rate of 12% of prescriptions for off-label uses. The percentage varied, however, by therapeutic class, ranging from 5% for ear, nose, and throat medications to 25% for central nervous system medications. An econometric model from the National Ambulatory Medical Care Survey estimated a 38% rate of off-label use.").

127. Asher Mullard, *2021 FDA Approvals*, NATURE (Jan. 19, 2022), https://www.nature.com/articles/d41573-022-00001-9#:~:text=The%20FDA's%20approval%20count%20last,at%2051%20drugs%20per%20year; Angelika Batta, Bhupinder Singh Kalra & Raj Khirasaria, *Trends in FDA drug approvals over the last 2 decades: An observational study*, *9* J. FAM. MED. PRIMARY CARE 105 (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7014862/; *Is it true FDA is approving fewer new drugs lately?*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/media/80203/download.

were approved" the first time they were submitted.[128] But this reflects only drugs that made it to the end of a very long process. While there is no official data, one commonly repeated estimate is that "[o]nly 5 in 5,000 drugs that enter preclinical testing progress to human testing. One of these 5 drugs that are tested in people is approved."[129] The result of this process, established by federal law and funded by Congress, is to limit the drugs available for sale in the United States to those which have been proven safe and effective for specific purposes. While the FDA neither initiates nor solicits companies to develop drugs, its standards guide the behavior of private drug companies in deciding which drugs to advance through development, first in the lab and then animal testing, before submitting an application for approval to begin testing in humans.[130] Moreover, the longer a drug is used off-label, the less likely that any such review will ever occur because there is little financial incentive to do so.[131]

D. Lack of Information Sufficient for Providers to Obtain Informed Consent from Patients

Physicians have a fiduciary duty to provide patients with enough information so that they can make informed decisions about their care.[132] In the case of prescription drugs, the information available to the physician is the FDA "label," which describes the purpose for which the FDA has issued approval in terms of the kind of condition to be treated and the category of patient.[133] Moreover, consumer research suggests that there is very little public awareness of the difference in what is known about the risks and benefits of a drug used off-label as opposed to one that has been FDA approved.[134]

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128. U.S. FOOD & DRUG ADMIN., ADVANCING HEALTH THROUGH INNOVATION – NEW DRUG THERAPY APPROVALS 2019 24 (2020), https://www.fda.gov/media/134493/download.

129. *See Drug Approvals – From Invention to Market . . . A 12-Year Trip*, MEDICINENET, https://www.medicinenet.com/script/ main/art.asp?articlekey=9877 (last updated July 14, 1999); *see also* U.S. FOOD & DRUG ADMIN., *The Drug Development and Approval Process*, https://www.fda review.org/issues/the-drug-development-and-approval-process (last visited July 26, 2020).

130. Susan Thaul, CONG. RSCH. SERV., R45792, OFF-LABEL USE OF PRESCRIPTION DRUGS 6 (2019) ("The FDA-approved labeling, which informs the clinician about dosing and likely and unlikely adverse events, helps protect the individuals for whom the drug is prescribed.").

131. *Id.* at 6 ("Once drugs are well established in off-label uses, manufacturers rarely design studies to determine or verify the safety and effectiveness of such uses.").

132. *The Fiduciary Relationship*, THE CLIMATE CHANGE AND PUBLIC HEALTH LAW SITE https://biotech.law.lsu.edu/books/lbb/x236.htm (last visited Apr. 8, 2022).

133. *Are Too Many Kids Taking Antipsychotic Drugs?*, CONSUMER REPORTS, (Dec. 2013), https://www.consumerreports.org/cro/2013/12/are-too-many-kids-taking-antipsychotic-drugs/index.htm.

134. *See* Jesse R. Catlin & Cornelia Pechmann, *An Investigation of Consumer and Doctor Regulatory Beliefs and Regulatory Knowledge about Pharmaceutical Drug Promotions*, 1 J. ASS'N FOR CONSUMER RSCH. 392, 403 (2016); *see* SUSAN THAUL, CONG. RSCH. SERV., R45792, OFF-LABEL USE OF PRESCRIPTION DRUGS 9 (2021) ("Most individuals, unaware of the nuances of FDA

This lack of information is exacerbated by the lack of any legal requirement that a physician inform a prospective patient that they are prescribing the drug off-label.[135] Without knowing that a drug has not been reviewed by the FDA for use to treat their condition, the patient may assume that their prescriber is fully informed about the risks and benefits of this particular drug for their specific condition.[136] As a consumer advocate testified in 2016 to an FDA panel on use of off-label medical devices:

> Patients should have informed consent, which includes signing a piece of paper that explains that the product is not approved by the FDA for the indication that the product is being prescribed for. It should also include a discussion of what that means regarding the lack of objective evidence that the benefits outweigh the risks for most patients.[137]

In the absence of legal requirements to inform, advice on the FDA's website that patients "may want to consider" asking their "healthcare provider . . . about using an approved drug for an unapproved risk" would only be relevant to patients whose provider chose to inform them.[138] As one critic puts it, unrestricted prescribing privileges are "an anachronism" in that it assumes all licensed prescribers have sufficient information to prescribe all FDA approved drugs.[139]

One of the consequences of an absence of a legal requirement to inform patients about off-label use is that very few doctors faced liability for harm attributable to the drug so long as they acted according to the prevailing standard of care.[140] Commentators on the risks to physicians of prescribing

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regulation, may not know that physicians may prescribe drugs for uses that FDA has not reviewed for safety and effectiveness.").

135. Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967, 967 (2007).

136. *Testimony to FDA Panel on Consideration of Off-Label Promotion of Medical Devices*, PATIENT CONSUMER & PUB. HEALTH COALITION (Nov. 10, 2016) http://patientsandconsumers.org /testimony-to-fda-panel-on-consideration-of-off-label-promotion-of-medical-devices/
(Jack Mitchell, the director of government relations for the non-profit National Center for Health Research, made the point that the issue was of even greater concern for medical devices than for drugs because "the vast majority" of approvals of medical devices are done without clinical trials).

137. *Id.*

138. *See Understanding Unapproved Use of Approved Drugs "Off Label,"* U.S. FOOD & DRUG ADMIN. (Feb. 5, 2018), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label (recommending seven "questions" that a patient "may want to consider" asking their "healthcare provider . . . about using an approved drug for an unapproved risks" which seek information such as "[w]hat scientific studies are available to support the use of this drug to treat my disease or medical condition?" available for FDA approved drugs being used for their intended uses but which are most likely unavailable for off-label use.).

139. Phillip M. Rosoff & Dorianne Lambelet Coleman, *The Case for Legal Regulation of Physicians' Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 659–60 (2011).

140. Katrina Furey & Kirsten Wilkins, *Prescribing "Off-Label": What Should a Physician Disclose?*, 18 AMA J. ETHICS 587, 590 (2016) ("Although many malpractice lawsuits have been filed on behalf of patients arguing that they did not give informed consent to take a drug because

hydroxychloroquine for COVID-19 concluded that they were low because "[t]he drug itself has been publicly available for 70 years and has been found to be safe with few side effects."[141] Therefore, a plaintiff would have to prove that whatever harm they experienced was because of the hydroxychloroquine rather than COVID-19.[142]

E. Distinguishing Off-Label Prescribing from Compassionate Use, Right to Try, Clinical Research Trials, and Emergency Use Authorizations

1. Right to Try/Compassionate Use

Off-label prescribing involves a drug already approved by the FDA, but patients often also seek access to drugs which have not been approved. Most often, these requests come based on information about a clinical trial of an experimental drug that has not yet completed the FDA process.[143] If the trial is still active, the patient's doctor can petition the FDA for permission to have access to the drug through its "Expanded Access" program.[144] The doctor must also seek permission from the company manufacturing the drug. In addition to the FDA and the company, the request must be approved by the Institutional

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they were not informed that use for their particular condition was actually off-label, the law has generally sided with physicians in finding that they have no legal duty to inform patients of a drug's regulatory status.").

141. Bernard M. Cassidy, *Off-Label Prescribing for COVID-19: Is it Fraud?*, LUBELL ROSEN, LLC, https://lubellrosen.com/news-resources/post/-label-prescribing-covid-19-it-fraud (last visited Aug. 2, 2020) (concluding that, when focusing on the CMS concern, the greater concern for those prescribing "Chloroquine" is that it may run afoul of Center for Medicare and Medicaid rules about reimbursement than about medical malpractice). *See also* Jennifer S. Bard, *Human Subjects Research in Emergencies: The Texas Nursing Home "Study" (Part II),* BILL OF HEALTH (Apr. 27, 2020), https://blog.petrieflom.law.harvard.edu/ 2020/04/27/human-subjects-research-hydroxy chloroquine-texas-covid19/#more-28705 (noting that it is likely that the "standard of care" for prescribing hydroxychloroquine would be the one at the time of treatment and doctors would not be held responsible for information that emerges later).

142. Melissa Pandika, *A Nursing Home Gave Over 200 Residents Hydroxychloroquine Without State Health Department Approval*, MIC (July 29, 2020), https://www.mic.com/p/a-nursing-home-gave-over-200-residents-hydroxychloroquine-without-state-health-department-approval-30267352 (reporting administration of hydroxychloroquine to two-hundred and five nursing home residents in Pennsylvania).

143. Patients also sometimes seek access to drugs which are no longer in the active process of approval, either because the sponsor has withdrawn the application or the FDA has rejected it.

144. Barbara K. Redman & Alison Bateman-House, *Institutional Review Boards as Arbiters of Expanded Access to Unapproved Drugs: Time for a Change?*, THERAPEUTIC INNOV. & REG. SCI., 1 (2016), https://www.researchgate.net/profile/Alison-Bateman-House/publication/293803863_Institutional_Review_Boards_as_Arbiters_of_Expanded_Access_to_Unapproved_Drugs_Time_for_a_Change/links/5a805fd80f7e9be137c8ef76/Institutional-Review-Boards-as-Arbiters-of-Expanded-Access-to-Unapproved-Drugs-Time-for-a-Change.pdf. The expanded access program requires an individual doctor to make application to the FDA and seek permission from the company manufacturing the drug. In addition to the FDA and the company, the request must be approved by the Institutional Review Board overseeing the study.

Review Board overseeing the study.[145] If the company and the FDA agree, the company can only supply the drug at cost since it is not yet approved for sale.[146]

Although the FDA has approved almost every request that it receives, patient advocacy groups have been very critical of the program.[147] These groups have been very successful in getting first individual states and now the federal government to broaden the availability of unapproved drugs by passing laws that purport to give drug companies additional permission that extend to patients investigational drugs at the very earliest stages of testing. These are called "Right to Try Laws" and, again, are intended to give patients access to drugs before they are approved for any use.[148] Whether these laws offer any additional benefit to patients is a matter of considerable dispute. The nation's leading bioethics expert on these laws, Professor Holly Fernandez-Lynch, has explained that "although terminally ill patients might assume they have nothing to lose by trying an investigational treatment, this is not necessarily the case . . . . They could take a medication that could make them die faster or in a worse way."[149]

Right to Try laws have attracted the same kind of criticisms as off-label prescribing because of concerns that the patients involved are very vulnerable to

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145. *Expanded Access: Information for Patients*, U.S. FOOD & DRUG ADMIN. (last updated Apr. 27, 2020), https://www.fda.gov/news-events/expanded-access/expanded-access-information-patients.

146. *Id*.; *Expanded Access and Right to Try: Access to Investigational Drugs*, CONG. RSCH. SERV. (Mar. 16, 2021), https://sgp.fas.org/crs/misc/R45414.pdf.

147. For example, an organization critical of the FDA's practices is called Right To Try, *see, e.g.*, https://righttotry.org/about-right-to-try/. *See* Mark Flatten, DEAD ON ARRIVAL: FEDERAL "COMPASSIONATE USE" LEAVES LITTLE HOPE FOR DYING PATIENTS 2 (GOLDWATER INST. ed., 2016), https://goldwaterinstitute.org/wp-content/uploads/2016/02/Dead-On-Arrival-Report.pdf ("[T]he entire system for gaining access to an unapproved medication is so rigged with bureaucracy and disincentives that it is bound to fail in most cases. Critics say it was designed that way, ensuring that only a tiny number of patients are able to navigate the complex, costly, and time-consuming maze that must be cleared just to file a compassionate use application for the FDA to consider.").

148. *Right to Try*, U.S. FOOD & DRUG ADMIN. (last updated Jan. 14, 2020), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try.

149. Jennifer Byrne, *Right to Try: A 'Well-Intentioned' but 'Misguided' Law*, HEMONC TODAY (Mar. 10, 2020), https://www.healio.com/news/hematology-oncology/20200303/right-to-try-a-wellintentioned-but-misguided-law. She also notes that pursuing an investigational treatment when there is really no hope that it will be effective could also mean "They might be losing valuable time with their families, or they might be missing out on palliative options." Arthur Caplan is another ethicist highly skeptical of Right to Try laws which he describes as "ballyhoo and hype" which are unlikely to help because "[t]he FDA does not make or control access to unapproved drugs. Those drugs are the property of the drugs' sponsors: companies and academic institutions and their investors. The FDA can't make them give anything to anyone." Arthur L. Caplan, *"Right-to-Try" Laws Provide Little Access to Investigational Drugs. We Created a Process that Does*, STAT (June 3, 2019), https://www.statnews.com/2019/06/03/effective-ethical-right-to-try-process/.

See Arthur Caplan, *"Right-to-Try" Laws Provide Little Access to Investigational Drugs. We Created a Process that Does*, STAT NEWS (June 3, 2019), https://www.statnews.com/2019/06/03/effective-ethical-right-to-try-process/.

over valuing the benefits and minimizing the risks.[150] Moreover, there is no real "right" granted by these laws since neither the federal nor state version impose any obligations on the manufacturers who control access. At best, these laws make access more attractive to manufacturers by providing them with immunity from negligence liability if the product causes harm and by prohibiting the FDA from using data generated by granting access as a reason to later grant approval.[151] In particular, there is concern that drug companies themselves are not obligated to share information they know about risks directly with patients.[152] Also, both Extended Use and Right to Try statutes require that the patient be very sick with no other options. There are no such requirements for physicians prescribing drugs off-label.[153]

2. Emergency Use

The Emergency Use Authorization process was developed by the FDA to accommodate the need of the Department of Defense to comply with a federal law that limits the ability of the military to administer off-label drugs and vaccines to active-duty personnel.[154] It allows the FDA on its own or at the request of the Department of Defense to temporarily change the terms of a label in order to make it available on an emergency basis. Although developed in response to the military's need to combat anthrax during the Gulf War, today it is available in any urgent situation where the FDA thinks it appropriate to avoid the consequences of off-label use. In the case of hydroxychloroquine, the FDA issued an EUA permitting its use so that the drug could be added to the national strategic stockpile. Individual physicians already had authority to prescribe hydroxychloroquine off-label. An EAU can also be issued to grant temporary approval to use a drug that has not yet been approved for any purpose.[155]

3. Distinction Between Clinical Trials and Off-Label Prescribing

Another pathway for a patient to get a drug before it is approved is to be enrolled in a clinical drug trial.[156] While there are certainly many barriers to entry to a clinical trial, such as those documented in the early days of HIV/AIDs

150. Jennifer Byrne, *Right to Try: A 'Well-Intentioned' but 'Misguided' Law*, HEMONC TODAY (Mar. 10, 2020), https://www.healio.com/news/hematology-oncology/20200303/right-to-try-a-wellintentioned-but-misguided-law.

151. Investigational Drugs for use by Eligible Patients, 21 U.S.C. § 360bbb-0a (2020).

152. *See* Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J. L. & MED. 361, 364 (2002).

153. IND Safety Reporting, 21 C.F.R. § 312.32 (2020).

154. *See* Jennifer Bard, *Why the Military Can Use Emergency Powers to Treat Service Members with Trial COVID-19 Drugs*, THE CONVERSATION (May 11, 2020, 7:49 AM), https://theconversation.com/why-the-military-can-use-emergency-powers-to-treat-service-members-with-trial-covid-19-drugs-135876.

155. *Id.*

156. *See* Noah, *supra* note 152, at 361.

drug development,[157] once enrolled, those taking experimental drugs are carefully monitored.[158] A participant in a clinical drug trial can only enroll after the proposed study is reviewed by an ethics board.[159] Part of that review involves assuring that the participant is fully informed of the risks associated with the drug under study, the options for seeking treatment outside the study, and the assurance that they can leave the study at any time.[160] Moreover, while they are enrolled, there is real-time monitoring for any "adverse events" experienced by any participant.[161]

III. FEATURES OF OFF-LABEL PRESCRIBING

A. How Do Pharmaceutical Company Market Off-Label Use?

Much of the available information about action by pharmaceutical companies to promote off-label use of their products comes from whistleblower complaints brought to the Department of Justice.[162] A study of these identified three main categories of actions taken by pharmaceutical companies to increase off-label use of their products.

A study of whistleblower complaints against pharmaceutical companies revealed many of the tactics used by pharmaceutical companies to extend the use of their drugs without running afoul of the prohibition against direct marketing. It found the companies worked directly with doctors to identify patients already in their practices who might be targets for off-label prescription.[163]

Based on existing research into the practices of pharmaceutical companies whose products are frequently used off-label, it is possible to see current efforts to promote off-label COVID-19 treatments by targeting not just the doctors who can freely prescribe them but the much larger group of patients who can ask for them.

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157. John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL'Y L. & ETHICS 299, 333 (2010) (citing the delays in FDA approval to the first HIV/AIDS drugs as a justification for allowing off-label prescribing).

158. *See* Noah, *supra* note 152, at 362.

159. U.S. DEP'T OF HEALTH & HUM. SRVS. OFFICE FOR HUM. RSCH. PROTECTIONS, INSTITUTIONAL REVIEW BOARD (IRB) WRITTEN PROCEDURES: GUIDANCE FOR INSTITUTIONS AND IRBS (2018), https://www.fda.gov/media/99271/download.

160. *Informed Consent*, U.S. FOOD & DRUG ADMIN. (July 2014), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent.

161. *Adverse Event Reporting to IRBs—Improving Human Subject Protection*, U.S. FOOD & DRUG ADMIN. (Jan. 2009), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adverse-event-reporting-irbs-improving-human-subject-protection.

162. Aaron S. Kesselheim et al., *Strategies and Practices in Off-Label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints*, 8 PLOS MED. 1, 1 (2011), https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000431.

163. *Id.* at 5.

B. What is the Patient Demand for Off-Label Drugs?

While there has long been concern that the involvement of pharmaceutical companies in patient advocacy groups encouraged the kind of information sharing that leads to requests for off-label prescriptions,[164] the size of COVID-19 market for off-label use of pharmaceutical products illuminates the issue to a brightness that can no longer be avoided.

To spend time in the world of those in need of compassionate use waivers for INDS or off-label use of an already approved drug is to be immersed in sorrow. It is a world of patients and families and doctors who in the face of serious pain, disability, and risk of death have tried all available options without finding any relief.[165] Some criticize that the pharmaceutical industry has encouraged patients to advocate for off-label use.[166] Patients have been encouraged to believe that the drug approval process is too cumbersome to allow testing beyond the minimum required for approval, but that based on the inside/deep knowledge of the company who invented the drug it can help those far beyond those for which it was first approved.[167] In a striking parallel to today's circumstances, in the late 1980s the world was confronted with the arrival of another deadly virus for which there was no effective treatment or vaccine. The process of developing effective drugs to combat HIV has been retold many times from many different perspectives. Moreover, by definition there was no available information on long term use. As John Osborn describes it,

> each public release of new long-term clinical data is eagerly anticipated and received at prominent medical conferences by

164. A 2017 article in the New England Journal of Medicine reviewed current concerns about the potential "conflicts-of-interest" related to promoting off-label prescribing which are present when "industry-supported patient-advocacy organizations have spoken out for access to drugs with questionable therapeutic benefit." Matthew S. McCoy et al., *Conflicts of Interest for Patient-Advocacy Organizations*, 376 NEW ENG. J. MED. 880, 880 (2017), https://www.nejm.org/doi/full/10.1056/NEJMsr1610625 (the article also considered another frequent concern about the extent to which these organizations were sponsored by pharmaceutical companies which was that these organizations "remained silent on policy proposals, such as drug-pricing reforms, that might benefit their constituents."). This article relies on a 2009 report by the Institute of Medicine calling for legislation mandating this disclosure. CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE (Bernard Lo & Marilyn J. Field eds., 2009).

165. Emily Kopp et al., *Patient Advocacy Groups Take In Millions From Drugmakers. Is There A Payback?*, WASH. POST (Apr. 6, 2018), https://www.washingtonpost.com/national/health-science/patient-advocacy-groups-take-in-millions-from-drugmakers-is-there-a-payback/2018/04/06/0a75f988-397b-11e8-af3c-2123715f78df_story.html; *see also* Elisabeth Rosenthal, AN AMERICAN SICKNESS: HOW HEALTHCARE BECAME BIG BUSINESS AND HOW YOU CAN TAKE IT BACK (2017).

166. Michelle Llamas, *Misplaced Trust: Why FDA Approval Doesn't Guarantee Drug Safety*, DRUGWATCH (Aug. 30, 2021), https://www.drugwatch.com/featured/misplaced-trust-fda-approval-concerns/.

167. Katharine Freeman, *Upsetting the Balance with 'Right to Try,'* PENN LDI (Jan. 18, 2018), https://ldi.upenn.edu/healthpolicysense/upsetting-balance-right-try; Howard Wolinsky, *Disease Mongering and Drug Marketing*, 6 EMBO REPS. 612 (2005)

> physicians who treat patients with HIV. With each release of data, there is a pattern of information migration that runs from the company to conference attendees, to publication in peer-reviewed medical journals in the United States and abroad, to submission by the company to various regulatory authorities around the world.[168]

The increasing research into the practice of off-label prescribing has found that these prescriptions are often not safe or effective. In contrast to prescribing a newly approved drug about which the only information is that presented to the FDA for approval, many drugs prescribed off-label are well known. For example, a recent study of psychiatric visits found that patients were being prescribed drugs to treat conditions despite existing evidence that they did not work.[169] They noted that for one drug in particular, trazodone, not only was its "efficacy . . . in the treatment of primary insomnia" weak, it also "has been shown to be associated with a higher risk of adverse drug events" than already approved FDA drugs.[170]

C. How Do Pharmaceutical Companies Make Money From Off-Label Prescribing?

At the time President Trump was hawking hydroxychloroquine, there were no vaccines available outside of a research study making the at-risk population equal to that of the population living on Earth. This dwarfs even the largest population of potential consumers of prescription drugs such as those with high blood pressure, diabetes, cancer, or depression.

Despite all the criticism of limiting off-label prescribing, attempts at self-regulation have failed because the practice is so lucrative. The pharmaceutical companies who make and market prescription drugs share with other entities an inherent financial interest in expanding the market for their products, but the legal compromise that allows off-label prescribing also imposes severe restrictions on their ability to promote uses beyond those already approved by the FDA.

The benefit of off-label prescribing is that it provides tremendous cost-savings to drug companies because it significantly reduces the always considerable cost of getting a new drug approved by the FDA.[171] With the option of off-label prescribing, they can test drugs on relatively healthy patients, who are unlikely

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168. John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL'Y L. & ETHICS 299, 333 (2010).

169. Aishwarya Vijay et al., *Patterns and Predictors of Off-Label Prescription of Psychiatric Drugs*, 13 PLOS ONE 1, 2 (2018) ("This practice is legal and common—a 2003 report showed that for the 3 leading drugs in each of the 15 leading drug classes, off-label use accounted for approximately 21% of prescriptions.").

170. *Id.* at 7.

171. Elizabeth Richardson, *Off-Label Drug Promotion*, HEALTH AFFS. (June 30, 2016), https://www.healthaffairs.org/do/10.1377/hpb20160630.920075/full/.

to die or experience inconvenient adverse events during the trial process with the knowledge that once it is approved, it can be prescribed widely.[172] This financial incentive to promote off-label use is of particular concern when there are safe and effective drugs available.

The true scope and nature of off-label prescribing is proprietary to the companies who stand to benefit financially: the companies that make drugs most frequently prescribed for purposes other than those for which FDA permission was originally obtained.[173]

The light cast on off-label prescribing by hydroxychloroquine's remarkable trajectory in first being hawked by the leader of the United States and then within months renounced by the FDA and the World Health Organization provides an opportunity to discuss a practice usually occurring in the shade cast by the protection pharmaceutical companies have for proprietary sales data.[174] As a result, specific information about which drugs are prescribed in the United States for purposes other than those for which they were approved by the FDA comes from the partial records available through government programs like Medicare or through surveys of doctors themselves.

D. Do Doctors Need the Privilege of Unrestricted Off-Label Prescribing to Provide Quality Patient Care?

Off-label prescribing has strong supporters among lawyers representing the pharmaceutical industry who often frame their articles as being on behalf of patients because the practice allows physicians to provide care consistent with their professional judgment.[175]

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172. JENNIFER KAO, PHARMACEUTICAL REGULATION AND OFF-LABEL USES 2 (2016), http://www.nber.org/aging/valmed/WhitePaperKao2_2017.pdf (reviewing "empirical evidence on pharmaceutical regulation and private investments from the health economics and health policy literature regarding off-label use"); *see also* Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1429 (2008), (discussing limits on the FDA and relaxation of oversight as well as the drug industry's exploitation of areas of ambiguity).

173. *See* Jerry Vorn Darrow, Jerry Avorn & Aaron S. Kesselheim, *FDA Approval and Regulation of Pharmaceuticals 1983–2018*, 323 J. AM. MED. ASS'N 164, 173 (2020).

174. *See* Francis Lamontagne et al., *A Living WHO Guideline on Drugs to Prevent Covid-19*, 372 BMJ 1, 2, 4 (2021), https://www.bmj.com/content/372/bmj.n526 (the World Health Organization issued a "Living Directive" that "recommend[ed] against the use of hydroxychloroquine as prophylaxis in individuals who do not have covid-19 (strong recommendation; high certainty evidence)").

175. James M. Beck & Elizabeth D. Azari, *Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 76–80 (1998); Rodney A. Smolla, *Off-Label Drug Advertising and the First Amendment*, 50 WAKE FOREST L. REV. 81, 87 (2015) ("Why do doctors so often prescribe medications for off-label uses? It cannot be that doctors do not know what they are doing, do not care for their patients, or have somehow been seduced or suckered by drug companies. . . . The most plausible intuitive answer . . . is that doctors prescribe medications for off-label uses because they have made the independent, professional medical judgment that the prescription, on balance, holds more promise of doing good for the patient than harm.").

But this is not necessarily how doctors themselves view it. A recent survey of board-certified internists found among 600 respondents that "60% of respondents felt that the FDA should 'definitely not' or 'probably not' allow off-label directly to physicians" with an even greater number endorsing the statement that "it would be a 'bad idea' or 'terrible idea' to allow off-label promotion in doctors' offices (71%) or in medical journals (68%)."[176] Their disapproval of the practice was based on concern that it may "increase prescriptions for drugs without meaningful benefits (61%; n = 416) and for diseases not previously considered medical problems (84%; n = 568)"; few saw off-label promotion as helpful with "[o]nly 30% of respondents" agreeing "that off-label promotion could improve clinical decisions."[177] Slightly under half of those surveyed (42%) endorsed an even stronger statement that "off-label promotion might actually worsen clinical decisions."[178] But their criticism of the FDA, for being too lax on off-label promotion, did not translate into a call to restrict the ability of individual physicians to prescribe off-label.[179]

Moreover, arguments against restricting off-label prescribing start from the false premise that it would be an exception to the unfettered freedom that physicians already enjoy. If this was ever true, it is not reflective of today's health care environment. Because the most expensive feature of the U.S. Healthcare System is the unrestrained cost of pharmaceuticals, biologics, and medical devices,[180] managing the cost of medications is a high priority for hospitals and public and private healthcare funders. Since Medicare does not cover out-of-hospital prescriptions, enrollees are encouraged to purchase additional prescription drug insurance from private companies which have their own formularies.[181] Whether it is imposed by managed care or hospital administrators, almost no doctors in the United States prescribe outside the parameters of a drug formulary.[182]

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176. Gayle Denney, *Majority of Doctors Think the FDA is Doing this Wrong*, MDLINX (May 8, 2020), https://www.mdlinx.com/article/majority-of-doctors-think-the-fda-is-doing-this-wrong/1F436iHEpIensIfjPNOytk (citing Jerry Vorn Darrow & Aaron S. Kesselheim, *FDA Approval and Regulation of Pharmaceuticals*, 323 J. AM. MED. ASS'N 164 (2020)).

177. *Id.*

178. *Id.*

179. *Id.*

180. Because the U.S. does not have a single-payer system, and has even legally prevented those running the systems for which the government does pay for like Medicare, Medicaid, and the Veteran's Administration from bargaining for prices. In some respects, we have allowed an ad hoc form of regulation by cost in which a doctor can prescribe anything, but a patient can only be reimbursed for a limited formulary.

181. *What Is a Prescription Drug Plan Formulary*, MEDICARE.COM (last updated Sept. 15, 2018), https://medicare.com/medicare-part-d/what-is-a-prescription-drug-plan-formulary.

182. The Petrie-Flom Center Staff, *Massachusetts Wants To Drive Down Medicaid Drug Costs: Why Is The Administration So Nervous?*, HARV. L.: BILL OF HEALTH (Apr. 6, 2018), https://blog.petrieflom.law.harvard.edu/2018/04/06/massachusetts-wants-to-drive-down-medicaid-drug-costs-why-is-the-administration-so-nervous/ ("Although drug formularies are ubiquitous in Medicare and the private insurance market, they're absent in Medicaid."); *Formulary*

Suggestions that regulating off-label prescribing would create an undue burden on health care provers also ignores the reality that both state and federal law restrict the prescribing of drugs that the federal government has identified as having potential to be abused outside of the healthcare setting.[183] The growing concern about deaths associated with opioid use has led to legislatures limiting provider prescribing authority to pursue societal public health goals. The result is that all 50 states and territories have now adopted some form of prescription drug monitoring programs (PDMP) to track individuals who are prescribed opioids by more than one provider.[184] As scheduled drugs, both the federal government and state governments have overlapping authority to impose limitations on both opioids intended to treat pain and opioid formulations intended to treat addiction.[185] Without endorsing the effectiveness of these programs or minimizing the horrifying and, perhaps, unintended consequences they have had on limiting access to opioids by those who need them the most, it is impossible to ignore the reality of their existence.

Finally, restrictions on off-label prescribing are often described as unwarranted criticisms of physicians themselves.[186] So much so that a 2011 article advocating "binding legal regulation" of physician's powers to prescribe off-label predicted that their argument "is new and will be controversial" because "society has a strong tradition of deference to physicians' autonomy and judgment in the context of the physician-patient relationship."[187] As a result of this deference, not only has "off label" prescribing "never been effectively

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Management, AMCP (July 18, 2019), https://www.amcp.org/about/managed-care-pharmacy-101/concepts-managed-care-pharmacy/formulary-management ("Formulary management systems are routinely used by health plans, pharmacy benefit management companies (PBMs), hospitals and government agencies, including the Veterans Health Administration, Department of Defense, and Medicare and Medicaid programs.").

183. *See* Controlled Substances Act, Pub. L. No. 91-513, 84 Stat. 1242 (1970) (codified as amended at 21 U.S.C. §§ 801–971 (2018)).

184. Joanne E. Brady et al., *Prescription Drug Monitoring and Dispensing of Prescription Opioids*, 129 PUBLIC HEALTH REP. 139, 140 (2014).

185. Following the much publicized death of Michael Jackson after being treated by his personal physician with Profonal, an aesthetic that can only be safely used in a hospital; the Drug Enforcement Agency considered adding it to the list of scheduled substances and restricting its use outside of hospitals. However, that did not happen. *Propofol*, DEA (2020), https://www.deadiversion.usdoj.gov/drug_chem_info/propofol.pdf; *DEA Weighs Limits for Drug in Jackson Case*, CBS NEWS (July 15, 2009, 5:32 PM), https://www.cbsnews.com/news/dea-weighs-limits-for-drug-in-jackson-case/; *DEA might tighten restrictions on sedative propofol*, CNN (July 16, 2009), http://edition.cnn.com/2009/HEALTH/07/15/propofol.dea.jackson/index.html.

186. Sandra H. Johnson, *Polluting Medical Judgement? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J.L. SCI. & TECH. 61, 64, 73 (2007) (citing Troyen A. Brennan et al., *A Social Science Perspective on Gifts to Physicians From Industry*, 290 J. AM. MED. ASS'N 252, 252–53 (2003); Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?*, 283 J. AM. MED. ASS'N 373, 373 (2000)).

187. Phillip M. Rosoff & Dorianne Lambelet Coleman, *The Case for Legal Regulation of Physicians' Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 659 (2011).

regulated, [t]o the contrary . . . even discussing such regulation is taboo."[188] In 2008, rejecting a then common view that off-label prescribing was due to financial incentives provided by pharmaceutical companies,[189] Sandra Johnson argues that "the prevalence of off-label prescribing" is not a result of low level bribery so much as it "is a manifestation both of learning patterns in the medical profession and deficiencies in the production and dissemination of clinical knowledge" which prioritizes information from other physicians more than medical journal articles.[190]

These arguments that restricting off-label prescribing are actual expressions of distrust, find some traction in an environment where medical training and practice leave physicians feeling unappreciated and burnt out.[191] The process of becoming a doctor in the United States is not just challenging, it is expensive and often brutal. With medical tuitions at some schools in excess of $100,000, doctors often graduate hundreds of thousands of dollars in debt only to find themselves locked into another three years of training at what seems, to them, the absurdly low salary of $60,000, on average.[192] As one popular commentator on the experience of new physicians explains,

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188. Philip M. Rosoff & Doriane Lambelet Coleman, *The Case for Legal Regulation of Physicians' Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 659 (2010); William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 247 (1993) (noting that "physicians attack some attempts to regulate medicine with the vigor of an artist resisting censorship" and that "[t]he medical community argues that overregulation chills innovation and reduces medicine to 'cookbook' therapy").

189. Most health insurance programs cover the cost of drugs prescribed off-label. For an example of the policy of a private company, *see Off-Label/Unproven Specialty Drug Treatment*, UNITED HEALTHCARE (effective Aug. 1, 2021), https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/off-label-unproven-specialty-drug-treatment.pdf.

190. Sandra H. Johnson, *Polluting Medical Judgement? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J. L. SCI. & TECH. 61, 64 (2008). Her claim is that the training practicing physicians receive inculcates a "universal skepticism . . . regarding the utility of scientific literature" in contrast to "clinical experience." *Id.* at 74–75. Therefore, they are more likely "to rely on opinions of respected peers and opinion leaders within the profession rather than on clinical studies or clinical guidelines standing alone." *Id.* at 76. She also notes that negligence standards that emphasize following "standards of care" promote reliance on seeking "safety in the herd." *Id.* at 81.

191. *See generally* Sharona Hoffman, *Healing the Healers: Legal Remedies for Physician Burnout*, 17 YALE J. HEALTH, POL'Y, & ETHICS 56, 67 (2019) (noting high levels of physician burnout in the U.S. "characterized by emotional exhaustion, negativity, cynicism, and a sense of lack of accomplishment and job fulfillment").

192. Keith L. Martin, *Medscape Residents Salary & Debt Report 2019*, (July 17, 2019), https://www.medscape.com/slideshow/2019-residents-salary-debt-report-6011735. It is important to note that while this vast amount of debt would be intimidating to anyone, it reflects a reality in which every graduate of an American medical school can expect to obtain a residency and after completion, a job that, on average, pays $200,000 in the first year. As one blogger explains, "despite the many unique issues physicians have to deal with, there is no reason for them not to be rich, eventually." *Why Aren't Doctors Rich?*, THE WHITE COAT INVESTOR, https://www.whitecoatinvestor.com/personal-finance/why-arent-doctors-rich/ (last visited July 26, 2020).

> "Physicians have struggled and sacrificed to develop the clinical judgment and skill needed to provide competent clinical care. They have undergone over a decade of schooling and training, taken on excessive student loan debt, worked backbreaking hours for low pay during residency, and risked their lives during the process. Yet when they have completed their training, they often times have to pay excessive malpractice premiums, having to answer to bureaucrats, administrators, insurance companies, politicians, and lawyers."[193]

The price of being a doctor has become even higher with the coming of COVID-19. As physician, poet, and author Dr. Colleen Farrell wrote recently in The Nation, the experience of doctors caring for patients with COVID-19 is analogous to those who watched their patients die of AIDS in the 1980s. Like them, she believes that she and her peers will be permanently marked by what they experienced. She writes:

> "Some of my colleagues describe what we have seen as war. Others call it a mass casualty event. I am still struggling to find the words to name it. But whatever we call it, I do not want to rush to heal from it. I need time to sit in the darkness and tend to the sorrow."[194]

E. Do Patients Need Off-Label Prescriptions?

Turning from doctors to patients, some argue that off-label prescribing is necessary because of the inherent slowness of the current drug approval process.[195] As a result, patients are harmed because they cannot get access to

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193. Christopher H. Loo, *How COVID-19 is Forcing Physicians to Rethink the Concept of Job Security*, KEVINMD.COM (May 5, 2020), https://www.kevinmd.com/blog/2020/05/how-covid-19-is-forcing-physicians-to-rethink-the-concept-of-job-security.html.

194. Colleen M. Farrell, *Witnessing the Pandemic From the Front Lines at New York City's Oldest Public Hospital*, THE NATION (July 13, 2020), https://www.thenation.com/article/society/bellevue-mourning-inequality-coronavirus/.

195. Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. L.J. SCI. & TECH. 61, 64 (2008) (arguing that the prevalence of off-label prescribing is not merely because of drug company efforts to increase profits but rather reflects "deficiencies in the production and dissemination of clinical knowledge"). "There were multiple barriers to clozapine access including prescriber-related barriers: lack of personal prescribing experience, concerns about clozapine blood monitoring and adverse effects; and institutional issues such as prescribers' adherence to evidence-based medicine principles and a local 'culture' of clozapine prescription." Hélène Verdoux et al., *Prescriber and Institutional Barriers and Facilitators of Clozapine Use: A Systematic Review*, 201 SCHIZOPHRENIA RSCH. 10, 17 (2018) (finding that the relevant factor in willingness of physicians to prescribe one anti-psychotic drug over another wasn't information but rather the prescribing practices of other physicians in their geographic area); *see* David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCH. INTERN MED. 1021, 1021 (2006) ("Off-label medication use is common in outpatient care, and most occurs without scientific support. Efforts should be made to scrutinize under evaluated off-label prescribing that compromises patient safety or represents wasteful medication use."); *see also* Monika K. Kryzanowska, *Off-Label Use of Cancer Drugs: A Benchmark is Established*, 31 J. CLINICAL ONCOLOGY 1125 (2013).

drugs they need.[196] The present issue remains that the current system incorporates no mechanisms for getting data of off-label prescribing practices back to the FDA in a form that might allow it to evaluate them for safety and efficacy. If a drug sponsor, physician, or anyone else has a good faith belief that an approved drug might be helpful in treating a condition other than that for which it was approved, the action most helpful to patients is to start a clinical trial.[197] So, for example, if hydroxychloroquine is already safe and effective for the population of people living with Lupus, then a clinical trial will show whether it is safe and effective for people infected with COVID-19. Also, developments in precision medicine have made it possible to assess treatments for safety and efficacy in so that it is no longer necessary to engage in guess work.[198] This reflects a reality that not all patients respond in the same way to the same treatment.[199]

The field of precision medicine is in its early days with advances being made quickly. It is increasingly popular to see patterns that were not apparent when studies were originally conducted. But if sponsors were required to generate information about the genetic profile of the patients in their studies, it would build a foundation on which to build later research that may extend uses.

IV. HOW OFF-LABEL PRESCRIBING BECAME ENTANGLED WITH FIRST AMENDMENT CLAIMS

Claims that pharmaceutical companies had protected first amendment rights to promote their products started to increase in frequency from the moment that the FDA first issued guidance suggesting that it would be illegal for pharmaceutical companies to promote off-label use of their products to physicians who could write legal prescriptions.[200]

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196. Sandeep Kumar Gupta & Roopa Prasad Nayak, *Off-Label Use of Medicine: Perspective of Physicians, Patients, Pharmaceutical Companies and Regulatory Authorities*, 5 J. PHARMACOLOGY & PHARMACOTHERAPEUTICS 88, 92 (2014).

197. Andre C. Kalil, *Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics*, 323 J. AM. MED. ASS'N 1897, 1898 (2020) ("It is imperative to discover new therapies, otherwise there will be no proven treatments for future coronavirus pandemics. By participating in an RCT, both patients and clinicians can benefit from the unique opportunity to directly contribute to the discovery of new therapies, and also from the safer monitoring process in the conduct of clinical trials compared with uncontrolled drug administration (whereby safety cannot be determined).").

198. A. Han et al., *The Promise of Big Data for Precision Population Health Management in the US*, 195 PUB. HEALTH 110 (2020).

199. *The Promise of Precision Medicine*, NAT'L INST. OF HEALTH (last reviewed Feb. 12, 2020), https://www.nih.gov/about-nih/what-we-do/nih-turning-discovery-into-health/promise-precision-medicine.

200. John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL'Y L. & ETHICS 299, 303 (2010) ("If the history of Western civilization may be seen as one long battle pitting order against freedom, the government's effort to curtail off-label speech might be dismissed as a minor skirmish on the outskirts of town. However, this issue is anything but minor in policy terms.").

A. Pharmaceutical Advertising as Commercial Speech

In a series of cases starting with *Pharmacy Board v. Virginia Citizens Consumer Council* in 1976,[201] the United States Supreme Court developed the principle that while advertising had not previously been protected under the First Amendment, it should be in order to maintain a "free flow of commercial information" so that consumers could make informed choices.[202] Under this theory which the Court has supported and continues to develop, both those making statements to market their products and consumers who might use that information to make purchasing decisions had a right to be protected against government restrictions.[203] Under what is now called the "Commercial Speech Doctrine,"[204] the government could only regulate truthful marketing of a legal product if it had a "substantial" interest that would be advanced "directly" by the restriction.[205]

In 2011, the United States Supreme Court in *Sorrell v. IMS* struck down a law restricting pharmaceutical manufacturers' access to the prescribing practices of individual doctors for the purpose of developing marketing strategies targeting doctors because it limited their ability to promote their products and therefore from exercising their right to free speech as protected by the Free Speech Clause of the First Amendment.[206] Seven years later, in 2018, the Second Circuit Court of Appeals in *United States v. Caronia*, cited *Sorrell* when vacating the criminal conviction of a pharmaceutical sales person who was found to have been discussing the off-label use of a drug with doctors who had the power to prescribe it.[207] The challenge to the Vermont law had been mounted by a coalition of business interests led by the Washington Legal Foundation (WLF), who brought suit in federal court claiming that the FDA guidance overstepped its congressional authority. Commenting on their victory, WLF characterized

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201. Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748 (1976).

202. *Id*. at 764–65.

203. *Id.* at 756 ("Freedom of speech presupposes a willing speaker. But where a speaker exists, as is the case here, the protection afforded is to the communication, to its source and to its recipients both. This is clear from the decided cases.").

204. For an overview of the development of the commercial speech doctrine, *see* David Schultz, *Commercial Speech*, FIRST AMEND. ENCYCLOPEDIA (2009), https://mtsu.edu/first-amendment/article/900/commercial-speech.

205. Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of New York, 447 U.S. 557, 564 (1980).

206. Sorrell v. IMS Health Inc., 564 U.S. 552, 557 (2011) ("Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment.").

207. United States v. Caronia, 703 F.3d 149, 163 (2d Cir. 2012); *see also* Lars Noah, *Banning Off-Label Drug Promotion Offends the U.S. Constitution: Making the Strongest Case*, 83 ALB. L. REV. 301 (2020) (applying the holdings of *Sorrell* and *Caronia* to explain why restrictions "on promoting off-label uses to bar generic drug manufacturers from touting uses newly approved by the FDA but only for their brand-name competitors cannot possibly pass muster under the First Amendment.").

the decision as a victory for patients because "[b]y prosecuting those engaged in truthful speech about off-label uses of medical products, the federal government has significantly hindered health care delivery in this country."[208] Michael Carvin, the attorney representing WLF, opined that "[o]ff-label use is essential to good medical practice because the medical community's knowledge of the drug effectiveness inevitably outpaces the painstaking FDA approval process for label changes. In many circumstances off-label use is standard-of-care medicine."[209] *U.S. v. Caronia* never produced a binding precedent beyond the Second Circuit because after losing, the FDA backed away and withdrew the offending guidance.[210]

Since then, the continuing movement to protect and promote off-label prescribing had become a proxy for a movement seeking to extend the constitutional protection for commercial speech even as the practice of off-label prescribing continued to be under critical review even before the president's advocacy for hydroxychloroquine.[211]

B. Pharmaceutical Companies Use of Social Media as a Venue for Promoting Off-Label Prescribing

Some suggest that one of the reasons pharmaceutical companies began funding disease-focused patient groups was to create opportunities for information about off-label use to spread among a community highly motivated to find information about their own industry.[212] Whatever pharmaceutical companies were able to accomplish through patient groups and physicians willing to be unpaid spokesmen, though, is a tiny fraction of what has become available in health and wellness communities of social media.

On January 15, 2020, an organization impressively named "the Association of American Physicians and Surgeons"[213] and a group of individual plaintiffs

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208. Thomas Sullivan, *United States v. Caronia: A Victory for Free Speech vs. Off Label Promotion*, POL'Y & MED. (May 6, 2018) https://www.policymed.com/2012/12/united-states-v-caronia-a-victory-for-free-speech-vs-off-label-promotion.html.

209. *Id.* For a recent overview of the issue, *see* Noah, *supra* note 207.

210. *See* Noah, *supra* note 207.

211. Joan H. Krause, *Truth, Falsity, and Fraud: Off-Label Drug Settlements and the Future of the Civil False Claims Act*, 71 FOOD & DRUG L.J. 401, 402–03 (2016) ("While the pharmaceutical industry may be losing the battle of public opinion, it is winning important victories in the war over First Amendment commercial speech protection.").

212. Laura Karas et al., *Pharmaceutical Industry Funding to Patient-Advocacy Organizations: A Cross-National Comparison of Disclosure Codes and Regulation*, 42 HASTINGS INT'L & COMP. L. REV. 453, 454 (2019), https://repository.uchastings.edu/cgi/viewcontent.cgi?article=1836&context=hastings_international_comparative_law_review.

213. *About AAPS*, ASS'N OF AM. PHYSICIANS & SURGEONS, https://aapsonline.org/about-aaps/. Founded in 1943 the organization describes itself as "a non-partisan professional association of physicians in all types of practices and specialties across the country." It describes its main role as fighting to "[p]reserve [m]edical [f]reedom" and help "[p]hysicians [r]educe and [e]liminate [t]hird [p]arty [i]nterference."

filed suit against Congressman Adam Schiff claiming that his efforts to get social media companies to stop spreading false information about COVID-19 treatment and vaccines was unconstitutional censorship.[214] They did so on the grounds that a letter he, a public official, sent to a private company, Facebook, had the effect of depriving the right of individuals "who seek access to vaccine information" to such information in violation of the First Amendment to the U.S. Constitution.[215] AAPS's lawsuit comes in the context of a vigorous public debate about the role of private companies that create websites where people can come together and talk about topics of mutual interest. Pharmaceutical companies may also be working directly with patients through their funding of what are usually called patient "advocacy groups." As Emily Kopp explained, "[t]he 'patient' voice is speaking with a pharma accent."[216] Despite numerous calls for regulation, and the example of such regulations from overseas, there is so far no obligation for any organization to report the extent of its support from pharmaceutical companies beyond the minimum required to maintain their tax-exempt status.[217]

CONCLUSION

President Trump's personal advocacy on Twitter and in public statements for the use of hydroxychloroquine to combat COVID-19 has had a destructive impact well beyond his term in office. While it may still be years before social scientists have fully identified the impact of his advocacy, the immediate rise in prescriptions has been thoroughly documented. But this initial impact which created shortages for those who depended on it to combat auto-immune disease was only the beginning of a cascade of negative consequences which included first subjecting people to the risks of taking a powerful drug of no benefit to them and then more broadly supporting a culture of rejecting FDA as a source of credible information. Again, only time will fully explore the extent to which this belief in the preventive and curative powers of hydroxychloroquine and ivermectin caused people to reject vaccines and effective treatments, early

214. Complaint at 4, Ass'n of Am. Physicians & Surgeons v. Schiff, No. CV 20-106 (RC), 2021 WL 354174 (D.D.C. Feb. 2, 2021), https://aapsonline.org/judicial/aaps-v-schiff-1-15-2020.pdf.

215. Ass'n of Am. Physicians & Surgeons, *Rep. Adam Schiff Sued by Physicians for Censoring Vaccine Debate* (Jan. 15, 2020), https://aapsonline.org/rep-adam-schiff-sued-by-physicians-for-censoring-vaccine-debate/.

216. Emily Kopp, *Patient Advocacy Groups Rake In Donations From Pharma*, KAISER HEALTH NEWS (Mar. 1, 2017), https://khn.org/news/patient-advocacy-groups-rake-in-donations-from-pharma/; McCoy, *supra* note 164, at 882; *see also* Susannah L. Rose et al., *Patient, Advocacy Organizations, Industry Funding, and Conflicts of Interest*, 177 J. AM. MED. ASS'N INTERNAL MED. 344, 348 (2017) (finding that 67% reported receiving industry funding as 11.9% "received more than half of their revenue from for-profit companies").

217. Susan Thaul, CONG. RSCH. SERV., R45792, OFF-LABEL USE OF PRESCRIPTION DRUGS 1 (2021).

evidence shows that many claim to have done so based on the President's statements even though he never explicitly advocated that they do so.

What is important for lawyers and policy makers today, though, is to look closely at the legislative structure that allowed the President's tweets about hydroxychloroquine and the social media advocates of ivermectin. The very public resulting rush to prescribe both of these drugs long after they had been definitively found to be ineffective provides an opportunity to re-consider unrestricted off-label prescribing. This article has not called for abolishing either off-label prescribing or even very broad prescribing privileges, but to evaluate their role in a world where healthcare is delivered very differently than it was during the 1950s when the FDA was given power to approve drugs. It has been more than ten years since Congress gave any serious consideration to off-label prescribing.

First, as an initial measure to promote fairness and transparency, prescribers could be obligated to inform patients that they are being prescribed a drug that has not been approved by the FDA for this particular use.[218] Second, rather than simply fight off-label prescribing by criminally investigating pharmaceutical companies who seem to be promoting its use, it would be more productive to create a pathway for off-label use by creating a streamlined process for the review of data supporting new uses of an already approved product.[219] As I have proposed in an earlier article regarding the reporting of post-approval adverse events, the cost of any registry system should be borne by the company sponsoring the drug since they are the ones who benefit financially when their drugs are prescribed off-label.[220]

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218. *Id*. at 9 ("Congress could require or work with the states to require that the prescriber inform the patient about the off-label use and describe the meaning of off-label use; the prescriber note in the prescription why the drug is being prescribed; or the pharmacist inform the patient that the use is off-label").

219. *Id.* at 9–10.

> Congress and other public policy groups consider whether and how to address off-label drug prescribing, they do not have adequate information on the scope and details of the practice. Congress could require or work with the states to encourage clinicians to note on prescriptions the reason for medication use (e.g., the specific condition, disease, or symptom), thereby allowing that information to appear in pharmacy databases, which would enable focused analysis of off-label uses; the establishment of confidential registries of off-label prescribing and follow-up information that FDA (or other designated scientifically appropriate agencies) could use in its electronic surveillance systems to identify associated adverse events and other drug use problems; or FDA to increase its surveillance of available data sources, such as registries and administrative and clinical databases, to identify patterns of off-label use and evidence suggesting effectiveness and associated adverse events.

220. Jennifer S. Bard, *Putting Patients First: How the FDA Could Use Its Existing Powers to Reduce Post-Market Adverse Events*, 10 IND. HEALTH L. REV. 495, 528 (2013) ("The central premise of this article is that the FDA should be using all its powers to develop systems intended to reduce the harm suffered by patients from problems that only emerge after a product is on the market. But within the reality of the FDA's funding base, it suggests that among these powers is

No one doubts the commitment of health care providers to their patients or their bravery. Nor should we ignore the administrative burdens all practicing healthcare workers face from a fragmented healthcare system and the stress they feel, whether warranted or not, from the threat of malpractice suits. But the existence of one bad system does not justify the existence of another. We should use this opportunity to identify and address the prescribing practices that have evolved to place, in general, no boundaries on physician prescribing and, in specific, a frequently used backdoor that allows drugs to be used without FDA review for safety and efficacy.

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the ability to shift the cost for these systems to those who stand to benefit financially from the product's success: its sponsor.").