Nikhil Dole

# Off-Label Prescriptions, Emergency Use Authorizations, and COVID-19

If you are at the start of a race, on a track you've never seen, against an opponent you've never met, you got to start running. The current SARS-CoV-2 (COVID-19) pandemic has shifted the world into an unprecedented era, which many currently alive have never experienced. This devastating illness has run rampant around the world as countries struggle to manage their populations, resources, and healthcare industry. Civilians are looking and hoping for the "miracle pill" to be developed that will wipe COVID-19 from the planet, however, many healthcare professionals in the U.S. and around the world are focusing on currently available pharmaceuticals for the solution. In past months, thanks in part to promotion from President Donald Trump, Hydroxychloroquine has been catapulted to the forefront of COVID-19 therapies. When a novel illness appears with little to no background information appears, the best strategy might just be to throw solutions at the wall to see what sticks. However, as the past and current data shows, this process still needs to be regulated, tracked, and properly documented if there is to be any real benefit. Without properly regulating the use and distribution of off-label medications during this crisis, the solution could turn out worse than the cure.

It is important to make the distinction between experimental and off-label drugs from the start. Experimental drugs are those which have not been approved in any capacity for use by the FDA while off-label drugs are medications that have been approved for one or more specific treatment, but are then prescribed for another by unapproved purpose by medical providers (Aronson and Ferner 2017). Off-Label Drug

Use (OLDU) is a common practice in the current medical field. About 1 in 5 prescriptions written by physicians in the U.S. are for off-label drugs (Wittich et al. 2012). Furthermore, physicians are not required to disclose to their patients when they have been prescribed an off-label drug (Meadows and Hollowell 2008). The frequency of these prescriptions also highly varies among specialties, the most notable of which is pediatrics (Wittich et al. 2012). One study reported that over 70% of pediatric patients leaving the hospital had at least one off-label drug prescription (Wittich et al. 2012). While this number is staggering, it is easily explainable as pediatric populations are often excluded from clinical trials and companies are not willing to fund the research. Another population with higher rates of OLDU resulting from exclusion from clinical trials are patients suffering from psychiatric disorders. If OLDU is so common, a natural question to ask is why these drugs have not been approved for the current off-label uses, considering some off-label drugs have become the standard of care. The process of FDA approval is not an easy path, even for drugs that have previously received approval for another use. Submitting any drug for approval can take around six years and cost close to two billion dollars (Meadows and Hollowell 2008). The process requires the four phases of drug trials to be done and even should all this be completed; the FDA approves only about 40-60% of drugs submitted for approval (Meadows and Hollowell 2008). However, once a drug is approved for one use, it can be used for other purposes, as long as it is prescribed by a physician. This can happen because of a law passed by Congress in 1997.

In 1997, Congress passed the Food and Drug Administration Modernization Act, which would restrict the FDA to regulating the production and sale of pharmaceuticals.

However, Congress included the caveat that the rules and regulations of the FDA cannot influence or impact a physician's duty to care for their patient (Meadows and Hollowell 2008; FDA.com). Congress ruled that the physician has the ultimate say when it comes to deciding which medications suit the treatment for their patient. The FDA also agreed with this sentiment by releasing a statement reinforcing the notion that the physician is the ultimate authority by publicly stating "once a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens", which includes populations not represented in the clinical trial or FDA approved (Meadows and Hollowell 2008).

While physicians should have a major say in the treatment decisions of their patient, it should not be assumed that the prescribing of off-label medications is always warranted. According to a study, 73% of all OLDU are supported with little to no scientific evidence (Radley et al. 2006). In some cases, the lack of supporting scientific evidence could be attributed to the general classification of the drug, as is in the case of some antibiotics, where physicians can use anecdotal and/or laboratory evidence to support their use and a full clinical trial is unwarranted. Likewise, there are numerous cases where physicians have prescribed a medication far from its approved purpose. Take the example of metaformin hydrochloride, originally approved for glycemic control in type II diabetes patients (Radley et al. 2006). For some patients, it has been prescribed to treat polycystic ovary syndrome (Radley et al. 2006). Though those physicians may have clinical reasoning to support the prescription, straying so far from the approved purpose may warrant its own approval. While it may be important for physicians not to be restrained by FDA regulations, it is also important to ensure the

safety of the patient. Rules and regulations not only protect patients, but the physicians as well. In a pandemic though, delayed action could result in the loss of lives, so are the regulations surrounding experimental and off-label drugs worth maintaining?

Pandemics require decisive and calculated action, so regulations surrounding drug approval can hinder the federal government response. In 2004, the 108th Congress passed the Project Bioshield Act, to set forth a plan to streamline the medical research and approval process in response to an emergency (Congress.gov; Nightingale et al. 2007). Under this Act, the Health and Human Services (HHS) Secretary is allowed to streamline the procurement of necessary products/services and this process is subjected to limited review of purchases and decisions (Congress.gov). Most importantly, the HHS Secretary can expedite “peer review procedures in certain instances, contracting with experts or consultant”, which allows the HHS Secretary to get an experimental or off-label drug approved much faster (Congress.gov). This authority has been condensed into the common term of Emergency Use Authorization (EUA) from which the HHS Secretary “can approve the emergency use of drugs, devices, or medical products that were previously unapproved by the FDA or the off-label use of approved products” drastically reducing the response time from the medical community (Nightingale et al. 2007). When the Project Bioshield Act is combined with the Defense Protection Act, the federal government can approve an off-label drug for a new use and ramp up the production of this medication to meet the needs of the pandemic. Project Bioshield is one of the most effective tools the HHS Secretary has at their disposal to handle a medical crisis in the U.S. and it is vital to understand the past uses of the Project Bioshield Act to evaluate the most effective way to tackle COVID-19.

In 2009, the H1N1 virus swept across America, causing the then HHS Secretary Kathleen Sebelius to declare a national pandemic. As part of the H1N1 response, Secretary Sebelius issued an EUA for the unapproved medication Peramivir, a newly formulated neuraminidase inhibitor (NAI) believed to be effective in the treatment of severely-ill patients (Sorbello et al. 2012). Currently available NAIs at the time were not formulated in the most effective way, especially for the pediatric and pregnant populations (Sorbello et al. 2012). Over 2100 five-day treatments of Peramivir were distributed to over 500 hospitals and then healthcare providers were asked to respond to a survey for epidemiological and clinical data on the efficacy of the new treatment (Pavia 2012). In the end, only 12% of clinicians responded to the survey, already highlighting a key flaw in the EUA of Peramivir (Pavia 2012). When a treatment is given EUA, there are no requirements for data collection or clinical observations. Adverse events and safety information are relayed to the HHS Secretary's office and the Secretary may periodically review the data, also having the opportunity to revoke a drugs EUA, should the Secretary deem it the right course of action (Nightingale et al. 2007). During the distribution and throughout the course of the peramivir treatments, valuable data concerning the drug's efficacy and the exact number of patients treated was lost. It is understandable that during a crisis, a physician's primary focus should be on the care of their patient, but the physicians should also be concerned whether or not the novel drug they administered to their patient is significantly more effective than the standard of care. The Project Bioshield Act is inherently designed not to be conducive to data gathering. Futhermore, the subjects chosen for Peramivir treatment were subject to selection bias as those patients selected were typically critically ill with risk factors for

influenza-related complications (Sorbello et al. 2012; Wester and Shetty 2016). Toxicology reports from those patients who passed away suggested that the administration of Peramivir late in the course of the illness was unlikely to have an effect on the outcome of the patient (Sorbello et al. 2012). This is another pitfall of the EUA of Project Bioshield; by choosing the severely affected patients, physicians are not evaluating the best treatment window for use of Peramivir and painting a false picture of its efficacy, especially when retrospective analysis concludes that the treatment was unlikely to affect patient outcome. Thus, there are conflicting reports on efficacy of Peramivir on H1N1. While some studies have reported that Peramivir is not a more effective treatment than currently available NAIs, others support a clear benefit. In an open-label, uncontrolled clinical trial on pediatric H1N1 patients in Japan, clinicians reported that Peramivir was statistically effective in reducing the infection period in children (Sugaya et al. 2012). Since then, Peramivir has been approved for treatment of Influenza A and B and has been shown to be an effective treatment for virus-strains resistant to other NAIs (Wester and Shetty 2016). While it is reassuring to hear that the EUA was able to rapidly distribute emergency treatment, it is concerning to see that years after the H1N1 pandemic, there is still confusion surrounding the effectiveness of the treatment.

The lack of requirements for data collection highlights a flaw in EUA that can have devastating consequences. Therefore, should an experimental or off-label drug be rapidly distributed without properly evaluating its efficacy in relation to the illness of interest, stringent data collection should be required. Even off-label drugs need strict

data collection regulations as the possibility of adverse events from the medication can be confused with unfamiliar symptoms of an unknown illness.

Ten years later and the COVID-19 pandemic has brought the world to a standstill. According to the CDC, there have been over 1.1 million cases of COVID-19 in the U.S. and 65,000 deaths since the start of the pandemic in late 2019. As the federal and state governments try to balance “flattening the curve” and handling escalating “Stay-At-Home” protests, many Americans are wondering when a miracle pill will arrive. Physicians across the country have been relying on OLDU as there are currently no FDA approved treatments for COVID-19. The off-label treatment that has received the most press is no doubt hydroxychloroquine. Through anecdotal evidence from early treatment in China, U.S. doctors identified hydroxychloroquine and chloroquine as viable treatments for COVID-19. One of the strongest pieces of support for hydroxychloroquine was a French study of COVID-19 patients that reported it as an effective treatment to achieve viral clearance (Gautret et al. 2020). This study supported the previously stated benefits of hydroxychloroquine in reducing viral replication reported by Chinese scientists in an open letter (Gautret et al. 2020; Cortegiani et al 2020). Furthermore the production costs for the medicine are low and it is already widely available as treatment for lupus and other autoimmune diseases (Cortegiani et al. 2020). A week later, HHS Secretary Alex Azar issued a EUA for hydroxychloroquine and has begun to distribute it from the federal stockpile (FDA.gov). With the EUA being issue, it is important to look back at the data since then and any new studies which have evaluated its effectiveness. The French study itself was clearly flawed as only 26 patients were treated with hydroxychloroquine and 6 treated with both

hydroxychloroquine and azithromycin (Gautret et al. 2020; Dahly et al. 2020). Furthermore, the subjects selected for controls versus intervention were different with varying demographics and without a similar baseline risk (Dahly et al. 2020). There are also concerns about the constitution of the control group as multiple members of that group were placed into the control group after not consenting to the study, in addition to being made up of patients being treated in different areas of France, highlighting a lack of standardized care between the two groups (Dahly et al. 2020). Yet with the potential of incomplete research, an EUA for hydroxychloroquine was issued. One month later and a new study conducted at the VA has reported that hydroxychloroquine might not be the savior drug that was promised. In a retrospective chart analysis of 385 male patients diagnosed with COVID-19, the study concluded that there is no reduction in patient mortality or reduction in the need for mechanical respiration when treated with either hydroxychloroquine or a combination of hydroxychloroquine and azithromycin (Magagnoli et al 2020). The study goes on to support that treatment with hydroxychloroquine is associated with an increase in patient mortality (Magagnoli et al. 2020). While like the previous study, there are concerns over selection bias in patients, it has presented a strong possibility of the Project Bioshield Act being used to authorize drugs with potentially harmful consequences. There are currently numerous clinical trials in progress around the world to validate the efficacy of hydroxychloroquine, but at the current moment, there remains a lot of conflicting anecdotal evidence. Peer-review randomized clinical trials are vital to properly evaluating and approving any treatment by the FDA and these regulations must not be thrown by the wayside in favor of a quicker

response and such actions can have devastating consequences, especially when there might be other drugs in development to fight COVID-19.

Companies around the world are racing for the COVID-19 cure. While the months of March and April were focused on hydroxychloroquine, the newest drug offering hope during these turbulent times is remdesivir produced by Gilead Life Sciences. Remdesivir is an experimental anti-viral drug that been placed on the same expedited track as peramivir. Currently, remdesivir is in phase III of the clinical trials process with studies in the U.S., China, and Japan (Gilead.com). These studies are evaluating the safety, efficacy in patients with mild to severe disease, and in those with pre-existing conditions (Gilead.com). Early research with *in vitro* models suggested that remdesivir had a significant effect on COVID-19 (Wang et al. 2020). This study identified remdesivir and chloroquine as the two front-runners in the treatment of COVID-19, however, as with chloroquine, the results have not translated as precisely into human models (Wang et al. 2020). Two months later, a double-blind, placebo-controlled, multi-center trial was conducted in China and the results indicate that remdesivir did not provide a statistically significant clinical improvement rates in adult patients (Wang et al. 2020). Furthermore, there was no difference seen between intervention and placebo groups in mortality rates, which were 14% and 13%, respectively (Wang et al. 2020). It is important to note that, while not statistically significant, those treated with remdesivir saw a reduced number of days for recovery (Wang et al. 2020). With remdesivir seemingly not providing a significant benefit, it is concerning to see that the CDC has already indicated that the FDA is working with Gilead to speed the drug approval process along. This may come from a recently

concluded federal clinical trial, which physicians spoke positively about at The White House saying that the results indicate a shorter recovery time, though the data has not been peer-reviewed as of yet (Voytko 2020). Since hydroxychloroquine did not live up to its reputation as the miracle drug, it is clear that the Administration may be taking a much more restrained approach to the rollout of remdesivir. With rising COVID-19 cases in the U.S., it begs the question on whether or not such restraint is necessary, especially since the approval by the FDA will not change its prescription to patients by physicians, provided remdesivir or a different treatment option receives EUA.

In times of crisis, there are established protocols to streamline the drug approval process that are outlined in the Project Bioshield Act of 2004. Rules and regulations can hamper the federal government from responding in quick manner, so what is the purpose of still requiring all drugs, experimental or off-label, to be subjected to the drug approval process or at least what is the purpose for maintaining strict guidelines? FDA approval is not only a validation of a drug's effects, but it is a major mark of confidence for the general public. During the H1N1 pandemic, researchers surveyed Americans on their opinions surrounding the government, FDA, and treatments. The study showed that 63% of respondents said they would not accept a new vaccine that was not approved by the FDA (Quinn et al. 2009). Even more distressing is that only 8.7% of people would willingly take the vaccine, the remainder being undecided (Quinn et al. 2009). This is a staggering figure as it highlights the amount of trust placed in the FDA approval process for medical treatments. The trust in the vaccine, government, and FDA also vary among races. The current COVID-19 crisis has shown that race is a important factor in a patient's outcome as data from Johns Hopkins University shows

that predominantly black counties have infection and mortality rates 3-fold and 6-fold, respectively, higher than predominantly white counties (Yancy 2020). With a clear and present danger to the African-American community, it is vital to make sure that the trust in the FDA and federal government is not eroded at such a crucial time. In that same survey, it was reported that African-Americans represented one of the largest populations undecided about accepting the unapproved vaccine (Quinn et al. 2009). However, when the drug has received EUA with FDA approval, 54% of respondents indicated they would accept the vaccine (Quinn et al. 2009). Almost six times as many people would accept the vaccine if it has gone through the shortened EUA process through the FDA in comparison to the 8.7% who would accept the unapproved vaccine. Unsurprisingly, the major overriding power over a patient's decision to take was the advice of their physician. 70% of respondents would take a drug or vaccine approved through EUA if it was dispensed or prescribed by their physician (Quinn et al. 2009). This statistic reinforces the notion that the highest trust comes from a patient's own physician. While regulations may hinder the quickest response to a crisis, they are not without purpose. The stamp of FDA approval is an important indicator to the general public about the validity of a treatment. Without it, patient adherence plummets to levels ineffective for containing a highly contagious and deadly virus.

The COVID-19 pandemic has undoubtedly changed the world in unforeseen ways. To get a grip on this crisis, physicians relied on one of the cornerstones of the medical practice, OLDU, to effectively combat the disease when there are no currently approved treatments. While in a normal scenario, there are debatable benefits and drawbacks to OLDU, but the lack of restrictions on medicine allow for a more versatile

response from the medical community. The Project Bioshield Act of 2004 loosens the regulations on the drug approval process in order to ensure that prospective treatments are able to be evaluated and tested in the quickest way. However, issuing EUA without caution can have consequences, as was seen in peramivir. The lack of coherent and cohesive data on the effectiveness of the treatment is a glaring oversight in the 2009 H1N1 pandemic response. It should not take five years for a regulatory body to evaluate whether or not an unapproved treatment was actually successful in its stated purpose and such negligence can cost lives. Already in the COVID-19 response, knee-jerk authorization hydroxychloroquine has shown that improperly evaluated treatments can not only cause shortages of medications for those who already need them, but promote drugs that are potentially more harmful than the standard of care. The federal government has corrected the course and taken a more controlled approach to the assessment and approval of remdesivir. Ensuring a drug's safety through stringent regulations is not only protecting patients, but also increasing the likelihood of the patient actually accepting the treatment. Though the regulations may slow down the response and Project Bioshield may circumvent many of them, maintaining the same strict criteria found in the FDA approval is essential to a coordinated national response. The unknown opponent already has a head start and the track is still unclear, but the U.S. unfortunately still has to play by the rules.

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