

FOCUS SPECIAL EDITION: THE IMPACT OF THE COVID-19 PANDEMIC

THE HUNT FOR AN EFFECTIVE TREATMENT OF COVID-19

(Sources: An article by Eric Palmer for FiercePharma, an article by Kevin Grogan for Scrip, and an article by Kai Kupferschmidt and Jon Cohen for Science Magazine)

As the world struggles to contain the COVID-19 virus, governments and pharmaceutical companies search for potential drug therapies to treat the virus while an effective vaccine is developed. This is no small task in the face of an enemy that is seemingly unstoppable in its rapid spread.

The World Health Organization (WHO) has launched a global megatrial called "Solidarity" which includes four promising COVID-19 treatments. The drugs included in the megatrial are already approved for other diseases while other unapproved drugs have performed with some success in fighting two other deadly coronaviruses known to cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).

There is hope that drugs that kill or slow COVID-19 (also known as SARS-CoV-2 or novel coronavirus) could save the lives of severely ill patients, and also be given prophylactically to protect healthcare workers and others at high risk of infection. Treatments may also reduce the time patients spend in intensive care units, freeing critically needed hospital beds.

The drugs being tested in the megatrial are *Remdesivir*, *Chloroquine* and *hydroxychloroquine*, *Ritonavir/lopinavir*, and *Ritonavir/lopinavir* with *interferon beta*. *Remdesivir*, originally developed by Gilead Sciences and designed to combat Ebola, shuts down viral replication by inhibiting a key viral enzyme, the RNA-dependent RNA polymerase. The drug was tested during the Ebola outbreak in Democratic Republic of Congo but did not show any effect. However, the enzyme that it targets is similar in other viruses and has shown promise inhibiting the coronaviruses that cause SARS and MERS. and has been used in individual cases of COVID-19 with promising results. More testing is necessary, as evidence from individual cases does not validate a drug's efficacy and safety. Gilead has made the decision to pull its drug from the open market for now due to the overwhelming product purchase requests for off label treatment of COVID-19 patients.

Chloroquine and Hydroxychloroquine, both anti-malarials, have shown encouraging results. The drugs have been used with success in China where Chinese researchers reported treating more than 100 patients. However, the underlying data has not been published. Subsequently, there have been (20) COVID-19 studies in China using the drugs, but again results are not readily available. There has also been positive anecdotal evidence of the drug's efficacy when used in conjunction with the widely-used antibiotic Zythromycin (commonly known as Z-Pak)

The WHO is engaging with Chinese colleagues with the promise of improved collaboration. Researchers in France have published a study involving (20) COVID-19 patients with

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IFPW Members Respond to COVID-19...

IFPW members are taking proactive steps within their organizations and with supply chain partners to develop the best response plans in light of the COVID-19 global pandemic. Here are some of those highlights...

- ◆ **AmerisourceBergen Corporation** has updated its active business continuity plans through the lens of this global pandemic. "In response to COVID-19, we are taking additional measures to protect our associates, our customers and the patients they serve. ABC distribution centers are taking extra measures for cleanliness given the volume of human health products that are processed through each facility and are using powerful EPA-approved disinfectants through electrostatic sprayers and standard spray canisters for 2-3 additional cleanings per day. ABC has proactively increased inventory on items related to COVID-19 treatment and supportive care, like IV fluids, generic injectables and related products for acute care providers, and essential medicines in other classes. AmerisourceBergen operates a 24x7x365 Global Watch Center (GWC) a centralized hub designed for responding to emergencies and crisis situations, and to protect the safety and security of our associates and operations and monitor for threats that may affect any of our global locations."

- ◆ **Bayer AG** is supporting hospitals in Lombardy, Italy, with a donation of one million euros. The money is being added to an aid fund that the regional authorities in Lombardy have set up to help procure urgently needed equipment for intensive care

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Finding Supply Chain Solutions for a Global Pandemic Through Blockchain

(Source: An article by Nishan Degnarain for Forbes)

As COVID-19 puts unprecedented strain on the global supply chain of nearly every product, most acutely on critical medical supplies, companies are converting supply chains to manufacture much needed personal protective equipment (PPE), COVID-19 test kits, and ventilators. These companies are stepping up around the world to address these critical growing shortages and exploding demand in the face of an overwhelming global pandemic.

Cases of the COVID-19 have significantly fallen in China and factories there are slowly coming back online. Multi-million-dollar contracts that typically take months to close are being inked within hours. However, one of the key bottlenecks has been the lack of trust between demand, supply and the essential financial mechanism. Governments and health systems have unique requirements for each system. For example, standards differ greatly from the European Union, the U.S. Food and Drug Administration, and non-EU standards. These standards are being updated almost weekly to allow for more supplies to come online to meet the forecasted demand.

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The Hunt (cont.)...

hydroxychloroquine and concluded the drug significantly reduced the viral load in nasal swabs. It was not a randomized controlled trial so results of the study face tough scrutiny. Still, companies including Bayer, Mylan and Teva are ramping up production of these drugs in anticipation of a positive outcome in testing and subsequent use in treating COVID-19. Significant donations of the drugs have also been made by manufacturers.

Ritonavir/lopinavir, sold under the brand name *Kaletra* by Abbott Laboratories, was approved in the U.S. in 2000 for the treatment of HIV infections. Abbott Laboratories developed lopinavir specifically to inhibit the protease of HIV, an important enzyme that cleaves a long protein chain into peptides during the assembly of new viruses. Because *lopinavir* is quickly broken down by the human body's own proteases, it is given with low levels of *ritonavir*, another protease inhibitor that allows *lopinavir* to persist longer. The combination drug can inhibit coronaviruses and has also been tested in SARS and MERS patients.

The first trial using *Ritonavir/lopinavir* with COVID-19 was not encouraging. Doctors in Wuhan, China gave 199 patients two pills of *ritonavir/lopinavir* twice a day plus standard care or standard care alone. While there was no significant improvement, researchers caution that the patients were very ill before being given the drugs, with more than a fifth of them expiring. This may be an indication that the drugs were given too late to help.

Ritonavir/lopinavir, given in concert with *interferon beta*, a molecule involved in regulating inflammation in the body, has also shown promise in small mammals infected with MERS. A combination of the three drugs is now being tested in MERS patients in Saudi Arabia and is the first randomized controlled trial of the disease. However, *interferon beta* may be risky when used in COVID-19 patients as it can lead to increased tissue damage if given too late in the disease's progression.

Other companies are also working tirelessly to find an effective way to stem the virus. Roche has launched a clinical trial of its arthritis drug *Actemra* after receiving backing from the government of China and is now working with the FDA to start a randomized, double-blind placebo-controlled phase 3 clinical trial to study *Actemra* in hospitalized patients with severe COVID-19 pneumonia. The drug, originally approved in the U.S. to treat rheumatoid arthritis has also been approved to treat cytokine release syndrome (CRS), a potentially fatal overreaction of the body's immune system in patients who received CAR-T cancer therapy. In some COVID-19 patients, a key indication of a worsening of the disease is CRS, or a more severe form known as a cytokine storm. Roche is ramping up production of the drug in a "powder in capsule" form in anticipation of positive outcomes.

Regeneron is collaborating with the U.S. Health and Human Services Agency to develop a treatment based on its past treatment for Ebola and MERS. Johnson & Johnson is also working with HHS to identify antiviral drug candidates that could potentially be effective in treating COVID-19. GlaxoSmithKline (in partnership with Clover Biopharmaceuticals) and Moderna are also working on a COVID-19 vaccine. Sanofi is seeking to repurpose its experimental SARS vaccine to target the virus. Pfizer has not jumped into the fray to date, but is considering working with its partner BioNTech to develop a COVID-19 vaccine.

Why Has COVID-19 Been So Virulent?

(Sources: An article by Ed Yong for *The Atlantic* and an article by James Gallagher for *BBC News*)

We've only known the deadly SARS-CoV-2 virus (otherwise known as COVID-19 and coronavirus) for approximately three months, but scientists have been able to make some educated guesses about where it came from and why it is behaving in such an extreme way.

One of the few mercies during this crisis is that, by their nature, individual coronaviruses are easily destroyed. Each virus particle consists of a small set of genes, enclosed by a ball of fatty lipid molecules. Because these lipid shells are so easily torn apart by soap, 20 seconds of handwashing can destroy the virus. These lipids are also vulnerable to the elements. A recent study demonstrated that COVID-19 survives for no more than a day on cardboard, and about two to three days on steel and plastic. There has been anecdotal evidence of a longer survival period for the virus, but essentially, the virus needs warm bodies to survive.

Previously, researchers and scientists have shared little interest in investigating coronaviruses, their origin and their pathologies. The 2002 SARS (Severe Acute Respiratory Syndrome) epidemic did elicit a slight increase in studies of this virus group. But with the emergence of COVID-19, the previous lack of interest is not a mistake likely to be repeated in the future.

COVID-19 is not the flu. It causes a disease with different symptoms and a different pathology that spreads and kills more readily. It also belongs to a completely different family of viruses which includes six other members, in addition to coronaviruses that affect humans. Four of them – OC43, HKU1, NL63, and 229E – have been mere annoyances for more than a century, a third of them being responsible for what has come to be known as the common cold. The other two – MERS and SARS (or SARS-classic, as some virologists have come to call it) are far more serious in their symptoms.

This seventh coronavirus exhibits a much more serious challenge, in that it spreads so readily from person-to-person, most likely due to the spikes projecting from the surface of the membrane which allow it to stick far more effectively than previously-known coronaviruses. The virus is also essentially two 'halves' which, when separated, causes the virus to activate. It is then that the virus enters a host cell. The bridge connecting the two halves is easily cut by an enzyme called furin which is made of human cells and found across many living tissues.

Scientists are also using specific techniques to examine the virus's genetic code and its sequencing from different patients to further determine a more detailed overall picture of how the virus is spreading. These techniques were also very helpful in identifying and following the outbreak of the superbug known as MRSA.

Currently, COVID-19 has manifested in two strains but shows signs of being slow to mutate. However it is a virus that easily made the jump from animals to humans, so an abundance of caution and study is required. The virus may still be adapting as part of its shift to infecting people and interacting with human immune systems. Scientists and researchers will continue to watch COVID-19 closely to follow its mutations. This will allow them to determine the best course of treatment and ultimately develop a vaccine.

Finding Supply Chain (cont.)...

These legacy procurement systems struggle to move at the pace the COVID-19 crisis demands resulting in countries around the world missing out on supplies. They cannot get financial mechanisms in place in a timely manner, a requirement which frequently needs to happen in hours, not weeks. Suppliers are insisting on cash upfront payments as they try to distinguish credible buyers from brokers and middle-men distributors. There have been widespread reports of fraudulent production and fraudulent claims across the medical and personal protective equipment supply chain. There are risks that equipment may not arrive in the right specifications at the right locations at the right time.

There are five trust challenges facing the medical supply chain, including:

1. *Product requirements.* Standards vary across health systems and countries, creating confusion for what each factory should be producing.
2. *Supply credibility.* There is uncertainty over which suppliers can produce equipment to the right quality, at the right production volume, at the right time.
3. *Financial payments.* Factories and freight companies are requiring financial payments be made upfront as their workers slowly come back online, and they themselves are trying to prioritize credible purchase requests.
4. *Customs certifications.* Customs certifications need to be rapidly validated to allow rapid transportation of equipment internationally, given that medical equipment is highly regulated.
5. *Transportation tracking.* Transport options need to be validated to ensure the right shipments can move from factories to airports to distribution centers to healthcare facilities.

Blockchain could play a vital role in the medical supply chain. Currently there is no centralized procurement system governed by a central body (as Central Banks regulate the financial system centrally.) Healthcare systems are unable to verify which ones have credible manufacturing capacities, traditional supply chains have been globally disrupted and suppliers are trying to distinguish credible purchasers or ensure that their production inventory will be purchased.

Blockchain can assist in the simplification and speed of the entire process by alleviating the lack of trust that exists with the current system in five steps:

1. *Production requirements.* Blockchain can provide a mechanism for health systems to continually update factories with the latest product requirements and specifications.
2. *Supplier credibility.* Blockchain can provide a way for health systems to credibly assess which factories have high quality control and can meet the specifications and production volumes needed.
3. *Financial payments.* Blockchain can act as a trade finance mechanism to ensure upfront blockchain-backed payments to factories that is then released as working capital upon pre-agreed production milestones and as supplies move to the next step of the supply chain.
4. *Customs certifications.* Blockchain-based customs certifications have been used to regulate export of many products from wildlife trade to pharmaceuticals and can be applied in this

instance as well.

5. *Transportation tracking.* Supplies need to be securely tracked around the world to ensure transparency in the supply chain, which can occur with blockchain-based provenance tracking.

The fight against COVID-19 is nothing short of a wartime effort on a global scale that requires innovative out-of-the-box solutions not seen in a generation requiring a committed effort now.

IFPW Members Respond (cont.)...

units in hospitals with the greatest needs. “Our emergency aid is designed to help support hospitals and hospital staff during the crisis,” stated The Chairman of the Board of Management, *Werner Baumann*. “Our colleagues in Italy are working with unbelievable commitment to maintain the supply of our medicines. On top of that, our emergency aid is designed to help support hospitals and hospital staff during the crisis.” Lombardy is by far the region of Italy worst affected by the corona pandemic. Hospitals there are reaching the limits of their capacity. In addition to Italy, Bayer has already sent considerable financial and material support to China to help contain the pandemic. Bayer will continue to provide affected regions and countries with rapid and unbureaucratic assistance as part of its corporate social responsibility.

- ◆ **GlaxoSmithKline** is contributing its science and expertise where it can have most impact and its scientists are working with international organizations including the WHO, *Coalition for Epidemic Preparedness Innovations (CEPI)* and governments worldwide. GSK is donating \$10 million to WHO and the UN Foundation’s *COVID-19 Solidarity Response Fund*. Additionally, the company is expanding its vaccines collaborations and a new collaborative research effort, the COVID-19 Therapeutics Accelerator, by making available compounds from its libraries for screening that could be used to treat cases of COVID-19. Finally, GSK is also donating surplus reagents to countries to support diagnostic testing, preparing to do the same for surplus personal protective equipment (PPE) and have initiated a volunteering processes for employees, to enable those with medical expertise to provide support to frontline health workers.

- ◆ **Johnson & Johnson** has a long-standing commitment to fight emerging epidemics and stands ready to support global efforts where it may make a difference. Developing preventive solutions for those who are most vulnerable to infectious diseases like coronavirus are J&J’s top priority. The company has established technologies and facilities that enable the creation, testing and scaling up of production for potentially transformational vaccines. J&J’s experience in helping to address epidemics, coupled with its expertise in respiratory illnesses, uniquely positions the company to address the latest coronavirus outbreak. J&J is actively engaged in developing new vaccines and treatments to address a wide range of infectious diseases that are already pandemics—such as HIV, hepatitis and TB—or that have pandemic potential, including Ebola, Zika and influenza. As a result of the work in these other disease areas, J&J is hopeful it can develop a vaccine for this virus by leveraging technology from the **Janssen Pharmaceutical Companies** of Johnson & Johnson and rapidly upscale production. This technology was recently

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used in the acceleration of the development and manufacturing of its investigational Ebola vaccine that is currently deployed in the Democratic Republic of the Congo and Rwanda. It was also used to construct the company's investigational Zika and HIV vaccine candidates. In order to meet the needs of the COVID-19 outbreak, we have a team of scientists working tirelessly on this effort right now.

- ◆ **Merck**, the maker of a range of medicines and vaccines for infectious diseases, is carefully monitoring the situation. Currently, none of its drugs are approved for use to treat COVID-19. As a science-driven company that aims to address some of the world's biggest health care challenges, it is carefully monitoring the situation and have established a team of scientists to assess internally available antiviral candidates and vaccine assets for potential to impact SARS-coV-2 and related viruses. While supply and demand vary by product, there are not any current impacts from COVID-19 on the production and supply of our medicines and vaccines for the U.S. Merck will continue to assess any increase in demand for its pneumococcal vaccine. Driven by Merck's steadfast commitment to patients, it is making every effort to ensure that patients in affected areas who are enrolled in clinical trials are able to continue their treatment and receive appropriate care and monitoring.

- ◆ **McKesson Corporation** is taking necessary steps to continue to supply its customers and protect employees. The company is in close contact with regulatory authorities around the world to ensure preparedness to address customer evolving needs. In order to support as many providers and patients as possible, for as long as possible, and to prevent hoarding, McKesson has placed some restrictions in place for personal protective equipment (PPEs) including limiting orders to only current customers and monitoring the amount being ordered. McKesson remains committed to getting critical supplies to customers who need them and is working with industry partners and government agencies such as the CDC, HHS, and FEMA to anticipate product needs. They are actively working with manufacturers, industry partners and government agencies to anticipate shortages and respond to unprecedented demand for certain medications and are taking a proactive approach to protect inventory and make sure provider partners have the supplies and medications they need to treat patients and help stop the spread of COVID-19.

- ◆ Due to the coronavirus pandemic, **Oriola Corporation** (Finland) has experienced high consumer demand for pharmaceuticals and pharmacy orders, particularly from Finland and Sweden. However, Oriola reports that the stock situation is good, and pharmaceutical import is working normally. To secure Oriola's deliveries to pharmacies, hospital pharmacies and veterinarians, it has taken in use all its picking and delivery capacity. Additionally, it has increased employee resources and operating time in logistics. Oriola's Kronans Apotek pharmacy chain in Sweden has restricted the sales of painkillers to three packages per customer to ensure availability to as many customers as possible. The company is closely following updates and instructions by the authorities in Finland and Sweden. Oriola recognizes its important role in society as it distributes

approximately half of the medicines in those countries. Oriola is included in the list of critical industries specified by the Finnish Government.

- ◆ **Pfizer** CEO, *Albert Bourla*, said in a statement "In this troubling time, Pfizer is committed to doing all we can to respond to the COVID-19 pandemic. Many companies, including Pfizer, are working to develop antiviral therapies to help infected patients fight this emerging virus as well as new vaccines to prevent infection and halt the further spread of this disease. Pfizer is working to advance our own potential antiviral therapies and is engaged with **BioNTech** on a potential mRNA coronavirus vaccine. We are committed to work as one team across the industry to harness our scientific expertise, technical skills and manufacturing capabilities to combat this evolving crisis"

- ◆ **Sanofi** CEO, *Paul Hudson* issues a statement, "Sanofi is committed to playing its part in the fight against the COVID-19 pandemic. We are focusing our response not only on prevention through the development of a vaccine, but also on treatment: yesterday, the FDA authorized a clinical trial program to assess whether an existing therapy from Sanofi and Regeneron approved to treat rheumatoid arthritis could be used as a safe and effective treatment for the symptoms of COVID-19. And to slow the spread of the virus, we have instructed all of our employees globally to work from home, with the exception of the incredible business-critical teams that ensure the manufacture and supply of medicines and vaccines that are essential to patients." Sanofi is focusing on four key areas where the industry can have both immediate and lasting impact – collaboration, prevention, treatment and manufacturing.

- ◆ **Walgreens Boots Alliance** is closely monitoring the pandemic of COVID-19 to ensure the safety and well-being of its colleagues, patients and customers around the world. In alignment with national health services and clinical and safety offices, leaders at the highest levels of the company are meeting regularly to assess the situation as part of a cross-functional, global emergency response team. Walgreens and Boots retail pharmacies have worked to provide up-to-date information and public health guidelines to customers, both in store and online. Clinical and safety offices are sharing the latest information from public health officials with their pharmacy team members, so that they are able to serve as a resource and help accurately address patient questions and concerns. WBA's wholesale business, continues to work with manufacturers and other partners in the supply chain to take the appropriate steps to meet the needs customers, including doctors, hospitals and pharmacies. Multi-skilled Business Continuity Teams have been put in place, managing steps to preserve the continuity of supply during a time of increased demand on health systems. WBA emergency response teams across the business are actively working to find ways for WBA and its wide network of health care and strategic partners to play a greater role in what has become a global emergency – including working with the United States federal government to expand access to COVID-19 testing.

(Sources: IFPW member press releases and company websites)