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CONTROLS TO MINIMIZE DISRUPTION OF THE PHARMACEUTICAL SUPPLY CHAIN DURING THE COVID-19 PANDEMIC

Cundell^{1*}, T., D. Guilfoyle², T. R. Kreil³, and A. Sawant⁴

¹Microbiological Consulting, LLC, Scarsdale, NY USA, ²Johnson & Johnson, New Brunswick, NJ USA, ³Takeda, Vienna, Austria, and ⁴Merck & Co. Inc., Kenilworth, NJ USA

The authors are members of the PDA COVID-19 Task Force.

*Corresponding Author: Microbiological Consulting, LLC, Scarsdale, NY. E-mail: tonycundell@gmail.com

ABSTRACT: This article reviews currently available scientific literature related to the epidemiology, infectivity, survival, and susceptibility to disinfectants of Coronaviruses, in the context of the controls established to meet Good Manufacturing Practice regulations and guidance, and the public health guidance issued specifically to combat the Covid-19 pandemic. The possible impact of the COVID-19 pandemic on the pharmaceutical supply chain is assessed and recommendations are listed for risk mitigation steps to minimize supply disruption to pharmaceutical drug products. Areas addressed include a brief history of the COVID-19 viral pandemic, a description of the virus, the regulatory response to the pandemic, the screening of employees, the persistence on inanimate surfaces, cleaning and disinfection of manufacturing facilities, use of GMP-mandated personal protective equipment to counter the spread of the disease, the role of air changes in viral clearance, approaches to risk assessment and mitigation. Biological medicinal products have a great record of safety, yet the cell cultures used for production can be susceptible to viruses, and contamination events have occurred. Studies on SARS-CoV-1 for its ability to replicate in various mammalian cell lines used for biopharmaceutical manufacturing suggest SARS-CoV-2 poses low risk and any contamination would be detected by currently used adventitious virus testing. The consequences of the potential virus exposure of manufacturing processes, as well as the effectiveness of mitigation efforts are discussed. The pharmaceutical supply chain is complex, traversing many geographies and companies that range from large multinationals to mid and small size operations. This paper recommends practices that can be adopted by all companies, irrespective of their size, geographic location, or position in the supply chain.

KEYWORDS: COVID-19 pandemic, SARS-CoV-2 virus, drug shortage, supply chain, employee screening, risk assessment, risk mitigation.

INTRODUCTION

During academic training, every microbiologist learns about pandemics and their impact on society. However, this bookish knowledge, although foundational, does not prepare one for all the potential contingencies and scenarios that a pandemic can present. As of writing this article, there is no approved drug to treat COVID-19 infection and a shortage of testing capabilities to identify the virus in people exhibiting symptoms of infection and screening for viral antibodies to determine infected individuals who have recovered and might have immunity and return to the work place. It should be noted that several Health Authorities have given emergency authorization for use of certain drugs and antibody tests. Further, due to global increase in demand, and disruption in transportation, the COVID-19 pandemic has resulted in major shortage of medicines needed to treat symptoms of the disease, manage pain or to prevent or control secondary infections. See Food and Drug Administration (FDA) Drug Shortage website for additional information (1). In addition, the pandemic has created a shortage of supplies of disinfectants and sanitizers, personal protective equipment (PPE) such as masks and gowns needed to meet GMP standards and associated Standard Operating Procedures (SOP).

Over the last 20 years, the world has experienced outbreaks of major novel respiratory infectious diseases such as SARS (Severe Acute Respiratory Syndrome) outbreak, (2002), Influenza pandemic H1N1 (2009), and MERS (Middle Eastern Respiratory Syndrome) outbreak (2012), and now the COVID-19 pandemic (2020). Pandemics can disrupt pharmaceutical supply in multiple ways at a time when medicines and vaccines are critically needed to control the pandemic and treat medical conditions in other patients not related to respiratory illness. Unavailability of raw materials, manufacturing supplies, shutdown of transportation systems and most importantly employee absenteeism due to infections, suspected infections, or fear of infections can disrupt supply. The U.S. FDA published *Guidance for Industry - Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products* (2) in March 2011, i.e., following the 2009 Influenza N1H1 pandemic. More recently, the Medicines and Healthcare Regulatory Agency, United Kingdom (MHRA) (3) and World Health Organization (WHO)(4) have published guidance on flexibilities in response to the COVID-19 pandemic. Since the last pandemic in 2009, there has been a massive global increase in the use of social media platforms as a source of information, which may or may not be accurate and can result in poor decisions that can impact the drug supply.

This article reviews currently available scientific information related to coronaviruses, disinfectants from peer-reviewed journals, authenticated sources such as the U.S. Federal Centers for Disease Control and Prevention (CDC), Food & Drug Administration (FDA), World Health Organization (WHO), major Health Authorities and national and international Good Manufacturing Practices standards. Although the article is primarily directed toward pharmaceutical drug manufacturing, the content should be useful to all manufacturers of over the counter drug products, consumer health products, cosmetics,

and medical devices. The question asked is how potential risks can be identified, and mitigated to protect our manufacturing facilities, employees, drug products, and customers from this pandemic respiratory virus? It should be noted that the COVID-19 pandemic is fast moving, and a tremendous amount of new scientific knowledge is being created every day. The authors have endeavored to make recommendations based on an anticipated progression of the pandemic in general terms, while the effect of the pandemic locally and internationally may vary. In addition, local laws, regulations and other requirements will inform each company's specific response to the pandemic.

Potential Risks that Can Result in Drug Shortages

The potential risk associated with COVID-19 can be categorized into i) direct risk posed by the virus to employees and to product and ii) indirect risk to manufacturing and distribution activities materialized by policies and controls promulgated by local, state and national governments to control the pandemic (Figure I).

To assess the direct risk posed by COVID-19, it is important to understand the epidemiology, infectivity, and susceptibility to disinfection.

Epidemiology of the COVID-19 Pandemic and Related Outbreaks

The 2019 novel coronavirus that was identified as the cause of an outbreak of respiratory illness is now referred to as the COVID-19 pandemic with the infectious viral agent designated as SARS-CoV-2. It was first detected in Wuhan, China on December 12, 2019 (5) and reported to the World Health Organization (WHO) China Country Office on December 31, 2019 (6). By mid-January, COVID -19 spread to Thailand, Japan, and Korea and then Europe.

As the rapid spread of COVID-SAR-2 in the USA is well documented in published literature the authors have used the US as the basis for discussion. The first documented U.S. case was a 34-year old man who travelled to Wuhan, China to visit family, returned and reported to an urgent care clinic in Snohomish County, Washington on January 19, 2020 in response to a health alert from the U.S. Center for Disease Control and Prevention (7). On March 11, 2020, the World Health Organization declared Coronavirus Disease 2019 (COVID-19) a pandemic (WHO Statement, 2020) as it had spread to multiple countries with high prevalence of community transfer. On January 31, 2020, the U.S. Federal Health and Human Service (HHS) issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS (8). In addition, on March 13, 2020, the President of the United States declared a national emergency in response to COVID-19 (9).

By the end of March there were 240,000 confirmed U.S. cases, with over 7,000 deaths, resulting in declaration of a national emergency by the President of the United States,

with orders for non-essential workers to work from home. By the end of April, there were over 1 million U.S. confirmed cases and 60,000 deaths. Pharmaceutical employees involved in production and testing activities are deemed essential globally; Health Authorities issued requests for pharmaceutical industry to work to avoid drug shortages.

Description of SARS-CoV-2 Virus

Coronaviruses are lipid-enveloped, single-stranded, positive sense RNA viruses, with 26 to 32 kilobases, belonging to the genus Coronavirus, which include several relatively benign, seasonal, common cold viruses and three new more virulent coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV), which emerged in the human population in 2003; Middle-East Respiratory Syndrome coronavirus (MERS-CoV), which emerged in humans during 2012; and SARS-CoV-2 that emerged in late 2019 and became COVID-19 pandemic in early 2020 (10, 11, 12)

Enveloped viruses like SARS-CoV-2 are highly susceptible to cleaning agents and disinfectants, above ambient temperature, and usually do not survive on inanimate surfaces beyond 2 days. This will be discussed in more detail in the section on persistence of SARS-Cov-2. The individual coronavirus particles are around 0.125 micron in diameter. N95 facemasks are rated capture 95% of particles down to 0.3 micron. This means that viral particles may still potentially get through this protection. The virus appears to be dispersed as larger droplets or aerosols and the multiple layers of the facemasks largely mitigates this risk. In contrast, HEPA filters are 99.97% effective at 0.3 micron and thus are much more efficient than facemasks.

Sources of the SARS-CoV-2 Virus

Zoonotic respiratory viruses initially emerge by animal-to-human and then largely by human-to-human transmission and to a lesser degree surface to human transmission. Dense human populations co-existing with dense chicken, duck, and pig populations as found in the People's Republic of China, as well of the consumption of wild animals as food, favors the emergence of novel respiratory viruses (13, 14). There is little or no evidence that the coronavirus is either a foodborne or waterborne viral pathogen.

Foodborne viral pathogens are responsible for a larger number of illnesses than bacterial pathogens annually. They may be classified into three main groups of viral illnesses; viruses that cause gastroenteritis, e.g., norovirus and rotavirus; enterically transmitted hepatitis viruses, e.g., hepatitis A; enteroviruses, e.g., poliovirus (15). Notably foodborne viruses are not associated with respiratory infection.

According to a March 2020 WHO Interim Guidance (16), although SARS-CoV-2 persistence in drinking water is possible, there is evidence from surrogate human coronaviruses that they are not present in surface or ground water sources or are transmitted through contaminated drinking water. The coronavirus being an enveloped virus, with a fragile outer membrane does not survive in the environment

and would be susceptible to filtration and chlorine treatment prior to water distribution.

Because SARS-CoV-2 may be shed in fecal matter (up to 10% confirmed presence in diarrhea) with some earlier reports of fecal-to-oral transmission (17, 18), this route of transmission should not be treated casually, and personnel hygiene emphasized in manufacturing facilities.

Public health experts have ruled out the possibility of insect to human transmission.

PERSONNEL HEALTH AND SAFETY

The biggest risk to the community at large, and as such to the pharmaceutical supply chain is human-to-human transmission of the coronavirus. Protecting the health and safety of employees should be the top priority of companies. The following points should be considered and as appropriate built into the pandemic response plans developed by individual companies.

Social Distancing and Work from Home

Certain local, state, and national governments and their health authorities have issued social distancing guidelines that may include mandatory stay at home order with a caveat to exclude 'essential employees,' i.e., employees necessary to keep critical services and activities in operation. To our knowledge, all governments combating the pandemic have classified 'pharmaceutical employees' as essential workers. As such, pharmaceutical companies generally have the liberty to determine what employees, if any, should work from home and who should report to work. The authors recommend companies develop a comprehensive contingency plan to identify essential activities and employees need to execute such activities. Support staff in quality assurance (QA), regulatory affairs, purchasing, human resources, research and development, planning, sales and marketing, and general management largely may work from home. Staff directly employed in manufacturing operations, quality control testing, engineering and maintenance, security, warehousing and shipping must be on site and potentially expose each other, facilities and products to viral contamination.

The employees identified as essential will depend on the manufacturing sites ability to conduct GMP activities remotely via a 21 CFR Part 11 compliant Information Technology (IT) system. For example, sites that have completely electronic batch records may not need to have QA batch record reviewer on site but those that have paper records, or hybrid paper and paperless systems may need to include such employee in the list of essential employees.

Furthermore, the determination of which employees are considered essential will depend, in part, on the level of community spread. For example, site auditors may not be considered essential, if the virus threat level is high within the local community but as the threat decreases auditors may be included in the list of essential employees.

Employees working off-site, using communication tools like mobile telephones, email, and video conferencing, can conduct many support activities in the pharmaceutical industry. This will significantly reduce the numbers of employees on site. In terms of the drug product supply chain, such employees may be viewed as non-essential while those employees (operators, as well as, managers) directly involved in product manufacturing, testing, and distribution viewed as essential. However, this distinction is not clear-cut. For example, it may be possible to delay a supplier audit of pharmaceutical ingredient used in the manufacture of an essential drug product; annual GMP training for packaging operators, or even marketed product stability testing. Determining what are non-essential activities and what are essential must be approached in a well-considered manner. The authors recommend that companies develop pandemic contingency plans that mandate essential activities and provide justification and timelines for the completion of activities that are delayed as non-essential. These plans should be approved by their quality control unit and may, importantly, be subject to regulatory review.

Identification of Infected Employees

As we believe that the biggest risk to the supply chain is person-to-person viral transmission followed by surface-to-person transmission, the most important risk mitigation will be excluding infected employees, especially those manufacturing, sampling, and testing drug products, from the pharmaceutical workplace to maintain the workforce and not potentially cause product contamination.

GMP regulations, for example 21 CFR 211.28 d states:

Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

As such pharmaceutical companies are required to have procedures in place and training program for employees to self-report and supervisors to observe and detect illness.

The major symptoms of Covid-19 infection are dry cough, fever, and difficulty breathing, but asymptomatic sufferers may shed the virus (19). All employees who self-identify as sick must be encouraged to stay home and report their status to their immediate supervisor and seek medical help. Examples of high-risk factors include sick family members and friends, recent foreign and domestic travel, attendance at events

with large crowds such as arena concerts and professional sport games, frequenting places-of-worship, schools, restaurants, social clubs and bars, dwelling in high-density population cities and towns, and commuting using public transportation.

To maximize the possibility that employees will self-report potential illness, the authors recommend reviewing sick-leave policies for all employees, including temporary and contract workers. We also recommend that companies enhance general awareness about the symptoms of COVID-19, by reinforcing the need for self-reporting and supervisory vigilance.

Screening Pharmaceutical Employees at the Point of Entry to Manufacturing Facilities

Recent epidemiological studies of COVID-19 suggest that infected individuals may remain asymptomatic or pre-symptomatic for up to 2 weeks (21). Therefore, in addition to reinforcing GMP requirements to self-report illness, companies should consider instituting procedures to screen employees entering manufacturing facilities. Such procedures need to be developed in accordance with government-mandated requirements and employee rights to privacy, avoidance of discrimination, and respect for existing employee contracts and union agreements.

On April 23, 2020, the U.S. Equal Employment Opportunity Commission (EEOC) issued an update to its guidance that now expressly acknowledges that employers may test employees for COVID-19 and conduct temperature-screening measures without violating the provisions of the Americans with Disabilities Act (ADA) or the Rehabilitation Act. According to the EEOC, “an employer may choose to administer COVID-19 testing to employees before they enter the workplace to determine if they have the virus.” Further, as stated by the EEOC:

Consistent with the ADA standard, employers should ensure that the tests are accurate and reliable. For example, employers may review guidance from the U.S. Food and Drug Administration about what may or may not be considered safe and accurate testing, as well as guidance from CDC or other public health authorities, and check for updates. Employers may wish to consider the incidence of false-positives or false-negatives associated with a particular test. Finally, note that accurate testing only reveals if the virus is currently present; a negative test does not mean the employee will not acquire the virus later.

The EEOC guidance applies only with respect to the two specified federal statutes in the U.S. We recommend that companies in the U.S. also consider the applicability of relevant state and local law and consult legal counsel as needed prior to initiating a mandatory employee-testing program. Companies outside the U.S. must obviously consider applicable national and local laws.

Also in the U.S., the Federal Occupational Safety and Health Administration (OSHA) recommends that companies develop an Infectious Disease Preparedness and Response Plan (22). The OSHA updated recommendations state the following:

If one does not already exist, develop an infectious disease preparedness and response plan that can help guide protective actions against COVID-19. Stay abreast of guidance from federal, state, local, tribal, and/or territorial health agencies, and consider how to incorporate those recommendations and resources into workplace-specific plans. Plans should consider and address the level(s) of risk associated with various worksites and job tasks workers perform at those sites.

How can employees be screened? Depending on the nature of the workforce, and the confidence and trust management has in the workforce, companies should decide whether to institute mandatory testing and/or institute self-screening or screening during entrance into the plant site.

If screening is performed during entrance to your plant sites, the employees' entry should be staggered to maintain social distancing and prevent delays. In addition to any mandatory COVID-19 testing that may be adopted, the authors believe in their expert opinion that the screening may consist of the following activities:

1. Monitor the body temperature of all employees. If self-monitoring is permitted, employees could check their body temperature using a personal clinical thermometer just prior to leaving for work. Employee should not report to work and seek medical advice immediately if the body temperature is above 100.4°F/38°C. If screening is conducted at plant entrance, trained screener should use a calibrated hand-held or wall attached no-touch thermometer. Employees with body temperature exceeding 100.4°F/38°C should be segregated and not allowed to enter the facility.
2. Conduct brief interviews of potentially SARS-CoV-2-infected employees to identify those with the common symptoms of fever, dry cough, and difficulties breathing.
3. Take a travel and contact history of suspected employee for the past 14-days to determine the potential for contamination of the manufacturing facility and infection of other employees.
4. Segregate any potentially infected employees and encourage them to get medical care through their regular physician or neighborhood medical center. It would be useful to provide employees with healthcare contact information.
5. Obtain a commitment from the employee to report their medical status and results of any testing for the presence of the coronavirus when they update their sick leave status according to company policy.
6. Determine whether the infected employee's co-workers within social distancing need to be quarantined from the workplace.
7. Determine the potential impact on the manufacturing operation as a result of employee absences.

8. When an employee is confirmed positive for the coronavirus, clean and disinfect the locations directly impacted in their workspace and other high-traffic areas like bathrooms, break rooms, hallway and entrances.
9. Review of the frequency of excluded employees by a local oversight committee to determine the need for self-quarantine of potentially infected employees, institute additional risk mitigations, and determine the potential impact to manufacturing schedule.

The recommended screening listed as 1 through 6 will have recognizable limitations. Multiple screening methods will most likely be more effective than a single method. Clinical thermometers may be in short supply during a pandemic. Studies on the use of infrared thermal image scanners in influenza and COVID-19 airport screening (23, 25, 25) to identify infected travelers compared to virus testing might detect less than half of those infected due to the viral incubation period and asymptomatic individuals. Screening each day of entrance to the workplace as compared to a departure or arrival screening at an airport will increase its effectiveness. A recent publication on the presenting characteristics of 5700 patients hospitalized with COVID-19 in the New York City area (26) found that only 31% had an elevated temperature, 17% rapid breathing, and 43% rapid heart rate. No information on the incidence of body ache and coughing was provided. This variability in symptoms will make screening more challenging. Based on these findings, companies are cautioned not to place too much reliance on only temperature screening. Another report from a Northern Californian hospital system indicated that chief symptoms presenting in the emergency department by 377 adults were 49% shortness of breath, 34% fever and 32% cough (27).

As testing for the SARS-CoV-2 viruses to detect infected individuals and the antibody to detect individuals who have been infected and recovered becomes widespread, companies should consider offering testing on a voluntary basis as an effective tool for keeping their workforce. Based on a PDA membership survey (In press) it appears that most employees would accept this offer of screening. The best method of managing this testing will become apparent as infectious disease experts gain more experience managing the pandemic and the subsequent return to work.

FACILITY AND PROCESS MANAGEMENT

Persistence of Coronavirus on Inanimate Surfaces

Human viruses cannot multiply outside the body and will not survive on inanimate surface for long. The analysis of 22 studies on the persistence of human coronaviruses other than SARS-CoV-2 virus (Table I) reveals they may persist on metal, glass or plastic for up to 9 days (Range 2 hours to 9 days) but they are readily inactivated by disinfectants and sporicides such as 62-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 minute (28).

The studies summarized in Table 1 have their technical limitations as they used related coronaviruses but not SARS-CoV-2, different types of inoculum preparations, high inoculum levels, different storage conditions, and RT-PCR assays as a measure of survival and not infectious units determined by cell culture methods. However, until additional studies are conducted with the SARS-CoV-2 virus these will be indicative and will contribute to our analysis.

Other agents used in the pharmaceutical industry, including antiseptics 0.05-0.2% benzalkonium chloride and 0.02% chlorhexidine digluconate are less effective requiring a contact time of up to 10 minutes (28). These findings will strictly limit the ability of novel coronaviruses to contaminate the pharmaceutical supply chain.

A more recent March 17, 2020 letter to the New England Journal of Medicine analyzed the aerosol and surface stability of SARS-CoV-2 (COVID-19) and compared this stability to SARS-CoV-1, its most closely related coronavirus (29). The authors of the letter reported 10 experimental conditions, conducted in triplicate, involving the two viruses in five environmental conditions, i.e. aerosols, inoculated plastic, stainless steel, copper, and cardboard. SARS-CoV-2 remained viable as measured by Median Tissue Culture Infectious Dose for 50% of the cells to be infected (TCID₅₀) in the aerosol suspension for the 3-hour duration of the experiment with a reduction in infectious titer from 10^{3.5} to 10^{2.7} TCID₅₀ per mL representing a half-life of 1.1 to 1.2 hours. In a controlled environment with many air changes per hour, the virus would be readily removed from the air.

The coronavirus was more stable on plastic and stainless steel than on copper and cardboard. Although the virus could be detected up to 72 hours, its titer was greatly reduced (From 10^{3.7} to 10^{0.6} TCID₅₀ per mL after 72 hours on plastic and from 10^{3.7} to 10^{0.6} TCID₅₀ after 48 hours on stainless steel). On copper, apparently due to Cu²⁺ toxicity, no viable SARS-CoV-2 was measured after 4 hours and on cardboard no viable SARS-CoV-2 was measured after 8 hours (29). This means, that in the event that controls established to exclude an infected employee fails, and in the event that packaged product is exposed to the virus, the plastic container used for primary packaging and cardboard used for secondary packaging should not carry infectious coronavirus, due to the amount of time the drug products will be advancing through the supply chain. Therefore, pharmaceutical products are very unlikely to pose any risk of infecting pharmacists dispensing, medical staff administering, and patients taking such products.

The relationship between temperature and relative humidity on the survival of coronaviruses in aerosols and on surfaces has been investigated. Enveloped viruses were found to survive longer at lower temperatures and humidity and may persist longer in refrigerators and cold rooms (30, 31, 32). The efficacy of pasteurization (63°C for 30 minutes) was demonstrated with MERS-CoV in camel, goat and cow milk with the virus titer reduced from 10^{5.5} to less than 10^{0.5} TCID₅₀ (33). Clearly, the heat sensitive SARS-CoV-2 virus will not survive sterilization processes used in sterile product manufacturing.

Inactivation of Viruses Due to Routine Cleaning and Disinfection

The coronavirus may be physically removed from a surface with a particle-free wipe, inactivated by detergents in cleaning agents, or inactivated by disinfectants and sporicides. In addition to routine cleaning and sanitization programs established to meet GMP requirements designed to protect product, companies should establish cleaning and sanitization of surfaces in non-GMP areas, including hallways, bathrooms, offices and other common areas, to protect the health and safety of employees during the pandemic. The controls, qualification and documentation requirements for GMP activities should be well established and subject to change control and/or planned deviation. Such controls are not required for sanitization programs designed for the non-GMP areas.

The frequency of cleaning and disinfection of an area in a GMP manufacturing facility will depend on the intensity of traffic in the area and exposure of personnel to drug product manufacturing. This frequency may range from weekly, to daily, to before and after each shift. It should be emphasized that cleaning to remove grime and product residues prior the application of disinfectants is critical for their best efficacy. Table II, although not exhaustive as the U. S. Environmental Protection Administration (EPA) List N contains 75 agents, provides useful information on representative commercially available products, their active ingredients, contact times and antiviral claims (34).

Cleaning and disinfection are considered critical GMP processing steps especially in sterile product manufacturing subject to process validation (See 2004 FDA Aseptic Processing Guideline). Guidance on the qualification of individual disinfectants and sporicidal agents may be found in USP <1072> *Disinfectants and Antiseptics* (35). Media reports highlight the shortage of disinfectants and hand sanitizers. Under the current circumstance, it is the expert opinion of the authors that on an interim basis, alternate suppliers may be identified and a like-for-like substitution made forgoing process validation and a vendor audit to make up for the shortage. Critical elements for making this like-for-like selection of an alternative source of a disinfectant include reputation of the supplier, active ingredient, active ingredient concentration, EPA and other national registration, efficacy claims, whether the disinfectant formulation is diluted prior to use, a ready for use product, and sterilized by gamma irradiation. To alleviate the shortage of hand sanitizers, the FDA has authorized the in-house production of alcohol hand sanitizers (36), but the authors believe that these materials should not be used in the critical ISO 5 aseptic processing areas.

Viral Clearance by HVAC systems and HEPA Filters in Cleanrooms

Warehouses, offices, laboratories, manufacturing and packaging areas in a pharmaceutical manufacturing plant will be served by heating, ventilating, and air conditioning (HVAC) systems to maintain targeted temperature, humidity, and numbers of air changes appropriate for each of these areas. In addition, clean rooms and other

controlled areas where sterile drug products are manufactured are supplied with High-Efficiency Particulate Air (HEPA)-filtered air to meet specified air cleanliness levels as well as more stringent requirements for temperature, relative humidity, space pressurization and number of air changes per hour to prevent product contamination.

In general, the level of environmental control, the Personnel Protective Equipment worn by cleanroom operators and the cleaning and disinfection program will make it unlikely that the coronavirus will persist in cleanrooms and contaminate sterile drug products (37). This leaves questions around areas served solely by conventional HVAC systems without HEPA filtration.

The 2014 American Society of Heating and Air-Conditioning Engineers (ASHRAE) Position Document (38) highlights that some infectious diseases including those caused by coronaviruses are transmitted through the inhalation of airborne infectious particles, which can be disseminated through buildings by pathways that include ventilation systems. This transmission may be reduced using dilution ventilation, directional airflow, room pressure differentials, source capture ventilation, air filtration and ultraviolet germicidal irradiation (UVGI), as well as appropriate cleaning and disinfection practices.

The ASHRAE document addresses control strategies (38). In a practical application, a combination of the individual interventions will be more effective than a single intervention in isolation. It is recommended that a heating and air-conditioning engineer be consulted on the implementation of these strategies. Pharmaceutical companies may consider improving particle filtration for central air handler, adding upper-room UVGI units, increasing the outdoor ventilation rates, and avoiding the use of lower ventilation rate motivated solely by reduced energy consumption.

Small aerosolized particles, <10 micron, generated by talking, coughing or sneezing will be suspended in the air and transported into the lower respiratory tract during breathing while larger drops 10-25 micron will fall through the air and accumulate on horizontal surfaces (39). Aerosols may be transported some distance by sideways airflows in non-classified rooms, whereas vertical laminar airflow with floor level exit registers will sweep the air clean in classified cleanrooms. Table III provides information on the number of air changes/hour.

We believe that pharmaceutical manufacturing conducted in classified areas (ISO 8 to ISO 5) will provide environmental conditions that will adequately clear viral particles potentially shed by employees. Non-classified areas where non-sterile drug products are manufactured and all packaging and labeling areas will need to be assessed for the number air changes (ventilation rate) to facilitate viral clearance and for their cleaning and disinfection practices. Based on this risk assessment, changes may be necessary.

Hand Sanitization

Hand washing and sanitization are an essential component of GMP controls designed to protect product. In addition to these routine controls, additional hand sanitization stations should be established in non-GMP areas to mitigate risk to employees.

Personal Protective Equipment

As COVID-19 infected individuals cannot be absolutely excluded from our manufacturing sites, personal protective equipment (PPE) will become more important. A decision should be made whether the workplace wearing of facemasks would be mandatory or limited to those activities in which personnel have direct contact with drug products. Table IV addresses the appropriate PPE to be worn during non-sterile and sterile drug product manufacturing.

The efficacy of different grades of facemasks in entrapping COVID-19 viral particles has not been fully established. The level of exposure to co-workers, processing equipment, and pharmaceutical drug products may determine the choice from homemade facemasks to cone masks, to medical facemasks to N95 grade facemasks (respirators).

The specifications for different grades of facemasks obtained from commercial supply catalogs may include:

- Certification Standards: Complies with ASTM F2299; ISO 9001.2015, and ISO 2859-3 1994; ISO 5 Compatible
- Bacterial Filtration: >92%, >95%, or >99% @ 1.0 micron particle size retention
- Reduced particle generation: Layers ultrasonically welded to limit particle shredding
- Effective Pore Size: 1.0, 0.45 or 0.1 micron
- Usage: Disposable, single use or re-usage
- Sterility: Non-sterile or sterile

FDA Regulation of Facemasks as Medical Devices

The FDA regulates facemasks and respirators when they meet the definition of a device under section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Generally, facemasks fall within this definition when they are intended for a medical purpose, including for use by health care professionals (41). These classifications are useful in determining which devices should be use in a pharmaceutical manufacturing facility.

The FDA defines these devices that may be suitable for use in a GMP manufacturing facility as follows:

Face Mask – A mask, with or without a face shield that covers the user’s nose and mouth and may or may not meet fluid barrier or filtration efficiency levels.

Surgical Mask – A mask that covers the user’s nose and mouth and provides a physical barrier to fluids and particulate materials. The mask meets certain fluid barrier protection standards and Class I or Class II flammability tests.

N95 Respirator – A disposable half-mask filtering face piece respirator (FFR) that covers the user’s airway (nose and mouth) and offers protection from particulate materials at an N95 filtration efficiency level per 42 CFR 84.181. Such an N95 FFR used in a healthcare setting is regulated by FDA under 21 CFR 878.4040 (FDA product code MSH) and is either a class II device that is exempt from premarket notification requirements under section 510(k) of the FD&C Act or is a class II cleared device.

NIOSH Approved N95 Respirator – An N95 respirator, approved by NIOSH that meets filtration efficiency level per 42 CFR 84.181.

The following are devices suitable for use in a clinical setting when medical staff treats COVID-19 infected patients but not in pharmaceutical manufacturing:

Face Shield - A face shield is a device used to protect the user's eyes and face from bodily fluids, liquid splashes, or potentially infectious materials. Generally, a face shield is situated at the crown of the head and is constructed with plastic to cover the user’s eyes and face.

Filtering Face Piece Respirator – A filtering face piece respirator (FFR) is a device that is a disposable half-face-piece non-powered air-purifying particulate respirator intended for use to cover the nose and mouth of the wearer to help reduce wearer exposure to pathogenic biological airborne particulates.

Surgical N95 Respirator – A disposable FFR used in a healthcare setting that is worn by HCP during procedures to protect both the patient and HCP from the transfer of microorganisms, body fluids, and particulate material at an N95 filtration efficiency level per 42 CFR 84.181. A surgical N95 respirator is regulated by FDA under 21 CFR 878.4040 (FDA product code MSH) and is either a class II device that is exempt from premarket notification requirements under section 510(k) of the FD&C Act or is a class II cleared device.

Given the CDC recommendation that in addition to social distancing, facemasks should be worn when people leave their places of residence, pharmaceutical companies should require employees reporting to work to be wearing facemasks and should supply non-medical masks to be worn on company premises until this recommendation is lifted. These facemasks would be replaced at least twice a day and disposed as potential biohazard waste.

In manufacturing areas where pharmaceutical ingredients, packaging components, intermediates, and finished products are exposed to workers, the PPE recommendations found in Table IV would be strictly followed.

Pharmaceutical companies as high volume users of facemasks may employ strategies to conserve these devices when they are in short supply. These include allowing employees to use home-made cloth facemasks to enter their facilities and continue to wear them in office areas, the removal of facemasks in isolated offices that maintain strict social distancing should be allowed, and, when strictly necessary, the re-use of surgical masks after decontamination. On April 9 2020, the FDA issued an Emergency Use Authorization (EUA) for the emergency use of a Steris Corporation vapor phase hydrogen peroxide sterilization system for decontaminating compatible N95 respirators for reuse by medical personnel to prevent potential exposure to pathogenic airborne particulates when the respirators are in short supply due to the COVID-19 pandemic. The data submitted by Steris supported up to 10 sterilizations and re-use. It was noted that cellulose-based facemasks are incompatible with hydrogen peroxide (42).

Vaccines against the SARS-CoV-2 Virus

The availability of safe and effective vaccines would help relax employee screening, social distancing practices and use of PPE in non-GMP areas. Greater than 40 different vaccines are in development globally with at least two now in Phase I human safety trials as of April 22, 2020. Vaccine clinical development is a complex process, which requires large clinical trials and establishing long term safety of the vaccine. The history of vaccine development is replete with examples of safety signals emerging post approval as a result of unexpected immunological response post immunization e.g. Rotashield and Dengvaxia. Further, it should be noted that there is no approved vaccine for SARS-COV-1 and for MERS, outbreaks that occurred in 2002 and 2012 respectively. Due to the widespread disease, recruiting large number of subjects for clinical trials is not expected to be a hurdle for COVID-19 vaccines, but this may change as the pandemic recedes. Despite all-out efforts Dr. Anthony Fauci, Director of the U.S. National Institute of Allergy and Infectious Diseases predicts that the availability of a vaccine will take a year to a year and a half, at least (43).

REGULATORY RESPONSES

Regulatory Response to the COVID-19 Outbreak

On Feb 11, 2020 when the WHO formalized the name of the current outbreak as COVID-19, the FDA immediately added this official disease on their website. This new FDA Webpage will soon fill up with a wide range of guidance documents and directives in a very short time. This COVID-19 outbreak has generated an unprecedented response from the FDA and other U.S. regulatory agencies to remove many regulatory hurdles that were hindering the Industry response efforts to monitor and treat this pandemic. These dramatic changes from the global compliance norm reflects the seriousness of this viral threat to our medical supply industry along with the safety of those who work in these industries and those who may be patients in need of these pharmaceutical

medical products. Among these U.S. federal agencies are the U. S. Food and Drug Administration, Center for Disease Control and Prevention, Occupational Safety Health Administration and the National Institution of Health. Their general contribution to the mitigation and relief of regulatory formalities will be briefly described below. In a February 14, 2020 press release the FDA announced that “if a potential shortage or disruption of medical products is identified by the FDA react swiftly to mitigate the impact to U.S. patients and health care professionals”. At this time period, the FDA press releases were focused on the impact of medicine and product coming from China due to the COVID-19 outbreak that was occurring in that area of the world. It is very unlikely at that time that the pharmaceutical industry or regulators knew how significantly the subsequent global pandemic would impact their routine activities. Subsequently, there has been a significant list of FDA initiatives to minimize the shortage of essential medicine within the U. S. because of active pharmaceutical ingredient (API) unavailability for the manufacturing of the finished products (FDA announcement date February 27, 2020). Included in this list are the following guidance documents and directives and their date of issuance:

1. Critical human drug shortages can be mitigated with lengthening the expiration dates. (FDA, February 27, 2020)
2. A new policy for certain laboratories that develop and begin to use validated COVID-19 diagnostics before the FDA has completed review of their Emergency Use Authorization (EUA) request (FDA, February 29, 2020)
3. The FDA and Federal Trade Commission (FTC) issued seven warning letters to companies for selling fraudulent COVID-19 products. The products cited in these warning letters are teas, essential oils, tinctures and colloidal silver. (FDA, March 9, 2020)
4. Coronavirus (COVID-19) Update: FDA issues Guidance for Conducting Clinical Trials. The FDA is aware that protocol modifications may be required, and that there may be unavoidable protocol deviations due to COVID-19. This would eventually include expedited early vaccine trial for the development of a COVID-19 vaccine (FDA, March 18, 2020)
5. FDA and National Institutes of Health (NIH) have begun a randomized controlled trial for the treatment of COVID-19 patients with the investigational antiviral drug Remdesivir, interleukin-6 receptor inhibitors as well as the application of convalescent plasma and hyper-immune globulin antibody-rich blood products that are taken from blood donated by people who recovered from the virus infection (FDA, March 19, 2020)
6. FDA provides a guidance document entitled “Temporary policy for preparation of certain alcohol-based hand sanitizer products during the public health emergency”. (FDA, March 20, 2020)
7. The FDA provides maximum flexibility to importers seeking to bring PPE into the U.S. with minimal disruptions during the importing process. The agency provided instructions to manufacturers on how to inform the U.S. Customs and Border Protection with specific advisement to expedite regulatory clearance. (FDA, March 24, 2020)

8. FDA issues an Emergency Use Authorization (EUA) to allow for the emergency use in health care settings of certain ventilators, anesthesia gas machines modified for use as ventilators, and positive pressure breathing devices modified for use as ventilators (FDA, March 27, 2020)
9. FDA establishes a new program to expedite the development of potentially safe and effective life-saving treatments. The program is known as the Coronavirus Treatment Acceleration Program (CTAP). This public-private approach is a cutting red tape, redeploying FDA staff and working day and night to review requests from companies, scientists and doctors who are working towards therapies. (March 31, 2020)
10. FDA issued a new EUA for non-NIOSH-approved respirators made in China, which makes KN95 respirators eligible for authorization if certain criteria are met. (FDA, April 3, 2020)

The authors of this review applaud the FDA in providing a more flexible regulatory response to the pandemic.

However, caution should be mentioned to the temporary nature of these allowable regulatory shortcuts during this pandemic and the return to standard practice should be documented to prevent any regulatory citations made by health authority inspections as the urgency of this historic event diminishes over time

European Union Regulatory Expectations during the COVID Pandemic

As with the FDA in the United States, we are seeing a strong regulatory response to the COVID-19 pandemic from other regions of the world (43). For example, the combined organizations of the European Commission (EC), Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) has published a Notice to their Stakeholders. The document is entitled “Questions and Answers on Regulatory Expectations for Medicinal Products for Human Use During the COVID-19 Pandemic” (EU Q&A document, April 2020). We will not discuss the entire Q&A in this review article, but we will highlight some key responses that the European Union (EU) expressed in their handling of deviations in manufacturing and importation of finished products and API as they relate to GMP and GDP issues during this pandemic.

Among some of the temporary changes include: (1) measures should be put in place to ensure the validity of GMP certificates that support manufacturer and importation of medicinal products into the EU should be extended to avoid disruptions in the availability of medicines, with a liberal time extension to sites located inside the EU; (2) With the difficulty to perform on-site GDP inspections, the validity of GDP certificates will be extended until the end of 2021 with no further company action required; (3) Remote batch certification and remote audits of API manufacturers have been expanded, even for those EU companies previously disallowed from this process and (4) In case of imports of investigational medicinal products from outside of the EU, the companies quality department should ensure that the quality of the batch is in accordance with the terms of the clinical trial authorization and meets EU GMP

requirements. The EMA recommended in order to make this assessment remotely, the companies need to review documents including batch records, in-process test reports, validation status of facilities, the results of any analyses performed after importation, stability reports, storage and shipping conditions, etc. Most gratifying was the responses to the question can quality requirements be waived/adapted for medicines intended to be used for the treatment of COVID-19 patients? The short answer to this question was “No” but with the EMA offer that if manufacturers were having difficulties to perform the compliance quality control steps, they were invited to contact the competent authorities and “to present an adapted control scheme based on a risk-based approach”. There was additional information to help navigate the regulatory hurdles posed by the restrictive travel conditions during this pandemic, so a review of the entire document is suggested for those manufacturing and conducting business in the EU geographic areas.

OVERALL RISK ASSESSMENT

Risk Analysis Tools

A number of risk analysis tools, including quality risk management, may be used when assessing risk factors. Tables V1–XI (See APPENDIX) show an example of a Hazard Analysis and Critical Control Points (HACCP) program approach (originating in the food industry), which summarizes the common inputs, identifies the various risks with ratings from low to high, and suggests common risk mitigations or critical process control points. Risk assessment of the specific steps in the supply chain for a representative non-sterile and sterile drug product, i.e., activity, risk level, critical control point, and mitigation are provided (44).

Steps analyzed included staff recruitment, procurement of pharmaceutical ingredients and packaging components, facility design and operation, cleaning and disinfection, utilities, manufacturing processes, packaging and labeling, warehousing, shipment, dispensing, and patient usage.

Drug Shortages

A major responsibility of the pharmaceutical industry and regulators is to anticipate and meet the changed demands for drug products driven by patient treatment and disruption to our supply chain. This statement appeared recently on the FDA website <https://www.fda.gov/drugs/drug-safety-and-availability/guidance-notifying-fda-permanent-discontinuance-or-interruption-manufacturing-under-section-506c-fdc>

“Due to the COVID-19 pandemic, FDA has been closely monitoring the medical product supply chain with the expectation that it may be impacted by the COVID-19 outbreak, potentially leading to supply disruptions or shortages of drug and biological products in

the U.S. The guidance, Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act, is intended to help applicants and manufacturers provide the agency with timely and informative notifications about changes in the production of certain drugs and biological products. In urging the submission of these notifications, the guidance may assist in our efforts to prevent or mitigate shortages of such products, including under circumstances outside of the COVID-19 public health emergency.”

Many pharmaceutical drug products have the potential to be in short supply due to increased demand to treat hospitalized COVID-19 patients. Shifting production schedules to meet this increasing demand will help but may create backorders for other needed drugs. The disruption to the supply chain due to absenteeism of production and testing personnel, warehousing and shipping of packaging components, pharmaceutical ingredients and finished products and imposition of national trade barriers to the free distribution of pharmaceuticals are all serious concerns.

Shortages have been reported for drugs that are used to keep patients’ airways open, as well as antibiotics, antivirals and sedatives (45, 46, 47). On March, 2020, orders for broad-spectrum antibiotics like azithromycin and antiviral like ribavirin have tripled; medicines for sedation and pain management like fentanyl, midazolam and propofol have increased by 100, 70 and 60% respectively.

Risk Assessment

The authors believe that as SARS-CoV-2 is a communicable human respiratory virus, the largest risk to the supply chain is absenteeism amongst line employees preventing the manufacture, testing and distribution of drug products and not product contamination. There are gaps in our knowledge on the epidemiology of the COVID-19 pandemic around identifying at risk populations and role of antibodies in preventing repeat infection that when filled will help manage our workforce (48).

The cell culture-based manufacturing processes of biological medicinal products can, and has in several instances been infected by viruses (49). The susceptibility of currently used manufacturing platforms, such as cell lines CHO, HT1080, and HEK 293 for the new SARS-CoV-2 has already been tested though, and the cell lines were found non-permissive, i.e. not support viral growth, to this new virus (Kreil, 2020 Pers. Com.). See Table V for a summary of the lack of capacity of the coronavirus to grow in commonly used cell lines.

The detectability of the new SARS-CoV-2 has also been tested, and the cell line panels used in standard in vitro adventitious virus testing as required by regulatory guidance (ICH Q5A (R1)) found capable of revealing virus presence (Kreil, 2020 Pers. Com.). As might have been expected from experience with the earlier SARS-CoV, the Vero cell line was highly susceptible to infection, which was easily visible by development of a

cytopathic effect (49).

The three main risks for viral contamination in cell culture for therapeutic production are the cell source, materials used in cell culture, and exposure of the process stream to the operators or environment with viral clearance, i.e., inactivation or removal from the product, being most important in reducing the risk of virus contamination of the finished product. The reader is referred to the Consortium on Adventitious Agent Contamination in Bio-manufacturing (CAACB) study for more details on risk mitigation (49).

DISCUSSION

The objective of our discussion will primarily focus on the unique current conditions and problems associated with the controls to minimize disruption of the pharmaceutical supply chain and to highlight other factors that we may not have had the available information to include in this review publication. Future data and experiences will eventually fill in the gaps of our current understanding and control of the COVID-19 pandemic.

The 2020 COVID-19 global pandemic meets all the characteristics of “A Black Swan” that the best-selling author Nassim Nicholas Taleb, defined as an event with low probability, extreme impact, unforeseen, and retrospective predictability (51). Dr. Taleb, a renowned Professor of Risk and Decision Science, proposed the Black Swan theory to explain highly improbable events, and the bias in decision making introduced by past experience, and by pockets of knowledge not available to all decision makers.

Low Probability Events

As per WHO, in 2016 Lower Respiratory Infections were the most deadly communicable disease causing 3 million deaths worldwide and was 4th overall on the top 10 global causes of death (52). As per CDC, in 2017 Influenza and Pneumonia was leading cause of communicable disease causing 55, 672 deaths in the U.S. and was the 8th overall on the top 10 causes of death (53). Although scientists understood the possibility of another novel highly contagious and deadly respiratory virus outbreak, past experience gained in managing SARS-COV-1, H1N1 Influenza, and MERS outbreaks i.e. limited spread may have introduced a bias among some scientists, policy makers, and public at large in accessing probability and underestimating the rapid spread of the COVID-19 outbreak into a pandemic.

Extreme Impact Events

The medical impact of a pandemic has been well studied by scientists, however the impact of mitigation strategies such as social distancing, and the impact of a global to transportation and resulting economic activity was perhaps not well understood and anticipated. As such, the scientific, medical, business and legal communities had to

scramble to find quick solutions and remedies to both the direct and indirect deleterious impact from this pandemic. The essential nature of the pharmaceutical industry to combat pandemics i.e. higher level of knowledge and awareness, regulatory requirement to have business continuity plans, regulatory relief, and GMP controls has resulted in relatively less impact on the manufacturing activities of pharmaceutical companies as compared to many other manufacturing and service industries.

Unforeseen Events

The complexity of the supply chain, increased demand for personnel protective equipment, the inability of essential employees to commute to work during stay at home orders were unforeseen domino effects. When national catastrophes (i.e., tornadoes, hurricanes, forest fires) occur in certain regions of a country there are generally local, state or federal contingency plans in place to mitigate or coordinate the multi-response to that effected area. Pandemics being relatively rare events, and each with unique characteristics and speed of spread can result in many unanticipated challenges.

Retrospective Predictability

As the pandemic progresses it is easy to connect the dots and conclude that the pandemic was predictable and different decisions were required. The fast spread of a novel virus requires decision-making on limited information and decisions need to be re-validated as new information becomes available. There needs to be a deliberate and educated infectious disease preparedness and response plan built into business continuity plans for the next inevitable pandemic.

Limited Viral Characterization and Transmission Factors

One of our knowledge gaps as it relates to this infections virus is our inability to identify asymptomatic, infected individuals and exclude them from the pharmaceutical workplace without widespread testing for the virus and its antibodies. This would be followed by the problem with a lack of follow-up contact investigations. Lastly, a more definitive assessment of the efficacy of personnel protective equipment especially facemasks against the SARS-CoV-2 virus is needed.

Current Industry Manufacturing Practices that are Low Risk

In general, due to the reduced ability of the lipid-enveloped virus to survive (but not proliferate) outside the human body, cleanroom environmental controls, cleaning and disinfection programs, and the personnel protection equipment employed in the pharmaceutical industry are adequate to prevent COVID-19 viral contamination of our sterile products manufactured in GMP-compliant facilities and do not need to be changed. Our review includes recent information that the COVID virus does not grow in the conventional manufacturing cell lines used for the proliferation and production of biologically based pharmaceutical products (Kriel, 2020 Pers. Com.)

Risk Mitigation Steps that May Need Re-evaluation

Areas that may need a closer risk assessment may be environmental conditions and controls in non-sterile product manufacturing rooms and all product labeling and packaging areas. The engineering and operational standards of the HVAC systems supplying these workspaces should be reviewed and, if necessary, improved. Parameters that may need to be assessed may include the number of air changes per hour, cleaning and disinfection programs, and the personnel protective equipment worn in these areas. Due to the low risk of viral contamination to our GMP-controlled pharmaceutical equipment and manufacturing rooms, no product testing for the presence of the COVID-19 virus is recommended. Until better understood, employees holding staff positions should work from home. Protocols for the eventual integration of the total work force back to pre-COVID-19 activity needs to be written and reviewed, which should include medical and legal staff to allow for the gradual and specific viral monitoring with a cognizant determination for those who are at highest risk to this virus. The reliability of the medical platform for making these determinations should be assessed. For example, the benefit of measuring antibody blood titers to the COVID-19 virus may not be a 100% reliable factor for preventing re-infection to this virus. (WHO reference. April, 25, 2020)

Critical Risk Mitigation Steps that should be Evaluated

Pharmaceutical companies must aggressively screen their employees for COVID-19 infection and remove those infected, in timely manner, from the workplace. These actions are necessary to avoid absenteeism due to continuing infection or re-infection of critical employees and the general work staff and a loss of employees to manufacture, test, and distribute essential drug products. A more definitive list of the risk mitigation steps recommended by the authors will be presented in the next section.

CONCLUSIONS

The authors, from their point-of-view as microbiologists, have attempted to review the risks and recommend mitigation steps that pharmaceutical companies, depending on their circumstances, should consider implementing in their manufacturing facilities. The PDA has established a COVID-19 task force with broader representation of the disciplines within our membership that expand on areas over and above this review.

Recommendations

The following risk mitigation steps to minimize the impact of COVID-19 on the pharmaceutical supply chain based on the risk classification in Figure I are recommended:

Direct Risks Posed By the COVID-19 Pandemic (Figure I)

Personal Health and Safety

- To facilitate social distancing employees able to do their job from home should be allowed to do so while employees directly involved in the manufacture, testing, packaging and distribution of pharmaceutical product should be screened for potential COVID-19 infection and if suspected to be infected should be excluded from the workplace.
- Non-essential visitors should be denied entry to all manufacturing facilities.
- Install additional hand sanitization stations in non-GMP areas.
- Wearing of facemasks by all employees in non-GMP areas should be considered after careful evaluations of the risks and benefits and would not be governed by GMP procedures.
- If a safe and efficacious COVID-19 vaccine is available, it should be made widely available to the manufacturing employees of pharmaceutical companies.

Product Quality

- Meeting GMP requirements related to Personal Protective Equipment and excluding at risk employees from manufacturing activities will provide adequate assurance.
- Testing for the presence of Covid-19 in manufacturing facilities and products is not recommended.
- Pharmaceutical GMPs should be strictly maintained.
- Determine if mammalian cell lines used for biopharmaceutical production are not susceptible to the COVID-19 virus.
- Pharmaceutical companies are encouraged to actively monitor recommendations from the U.S. CDC, FDA, EMA and the WHO and make changes to their policies and procedure as the COVID-19 pandemic recedes.

GMP Manufacturing

- Environmental controls, the appropriate use of personnel protective equipment, and cleaning and disinfectant practices, especially in warehouses, non-sterile manufacturing areas and packaging lines should be reviewed and updated where necessary.
- Manufacturing and testing schedules can be adjusted and additional shifts added to facilitate social distancing and to ensure essential drug products are not in short supply.

Availability of Supplies

- Strategies for conserving facemasks and other personnel protective equipment should be implemented.
- Enhance collaboration with suppliers educating them of their importance to the pharmaceutical industry.

Indirect Risks posed by the COVID-19 Pandemic (Figure I)

Availability of Employees

- Re-purposing employees for critical activities.
- Supply alternative transportation for employees commuting using public transportation to work.

Transportation Infrastructure

- Distribute finished goods using dedicated transportation in place of common carriers.

Availability of raw materials, e.g., drug substances, excipients, solvents, processing supplies, packaging materials.

- Strengthening existing supplier relations.
- Seeking alternative suppliers.

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DISCLAIMER

The opinions and suggestions made by the authors in this manuscript do not necessarily reflect the policies and requirements of their affiliated company

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Tables

Table I: Persistence of Coronaviruses on Inanimate Surfaces (28)

Type of Surface	Virus	Inoculum (Viral Titer)	Persistence (Temperature)
Steel	MERS-CoV	10^5	48 h (20°C) 8-24 h (30°C)
	HCoV	10^3	5 d (21°C)
Aluminum	HCoV	10^3	2-8 h (21°C)
Wood	SARS-CoV-1	10^5	4 d (RT)
Paper	SARS-CoV-1	10^6	24 h
		10^5	3 h
		10^4	< 5 min (All at RT)
Glass	SARS-CoV-1	10^5	4 d (RT)
	HCoV	10^3	5 d (21°C)
Plastic	SARS-CoV-1	10^5	≤ 5 d (22-25°C)
	MERS-CoV	10^5	48 h (20 °C)
	SARS-CoV-1	10^7	6-9 d (RT)
	HCoV	10^5	4 d (RT)
Polyvinylchloride	HCoV	10^7	2-6 d (RT)
Polyvinylchloride	HCoV	10^3	5 d (21°C)
Silicon Rubber	HCoV	10^3	5 d (21°C)
Surgical Glove (Latex)	HCoV	5×10^3	≤ 5 d (21°C)
Disposable Gown	SARS-CoV-1	10^6	2 d
		10^5	24 h
		10^4	≤ 8 h (all at RT)
Ceramic	HCoV	10^3	5 d (21°C)
Teflon	HCoV	10^3	5 d (21°C)

MERS = Middle East Respiratory Syndrome; HCoV = Human Coronavirus; SARS-CoV-1 = Severe Acute Respiratory Syndrome

Table II: Anti-virus Activity of Representative Commonly-used Disinfectants and Sporicidal Agents in the Pharmaceutical Industry (34)

Active Ingredient	Product Name	Company	Contact Time (Minutes)	Formulation Type	Emerging Anti-viral Claim
Hydrogen Peroxide	Accel (Concentrate)	Virox Technology	5	Dilutable	Yes
Phenolic	LpH	Steris	10	Dilutable	Yes
Phenolic	Vesphene II se	Steris	10	Dilutable	Yes
Sodium	CloroxPro™	Clorox	5	Dilutable	Yes

Hypochlorite	Clorox® Germicidal Bleach	Professional Product Co.			
Isopropyl alcohol	DECON-AHOL WFI® Formula 70%	Veltek Associates	NA	RTU	No
Hydrogen peroxide and peracetic acid	DECON-SPORE 200® Plus	Veltek Associates	NA	RTU	No
Quaternary ammonium; Ethanol	Lysol® Disinfectant Spray	Reckitt Benckiser LLC	5	RTU	Yes
Hydrogen Peroxide	Oxy-1 Wipes	Vorox Technology	0.5	Wipes	Yes
Ethanol	PURELL Professional Disinfectant Wipes	GOJO Industries	5	Wipes	Yes
Sodium Hypochlorite	Clorox Healthcare® Bleach Germicidal Wipes	Clorox Professional Products Co.	3	Wipes	Yes

See EPA List N: Products with Emerging Viral Pathogens and Human Coronavirus Claims (34)

Table III: Air Velocity and Number of Air Changes per Hour in Cleanrooms (39)

Class of Cleanroom	Airflow Type	Average Velocity (ft./min.)	Air Changes/hr.
ISO 8 (Class 100,000)	N/M	1-8	5-48
ISO 7 (class 10,000)	N/M	10-15	60-90
ISO 6 (Class 1,000)	N/M	25-40	150-240
ISO 5 (Class 100)	U/N/M	40-80	240-480

N = Non-unidirectional; M = Mixed Airflow; U = Unidirectional. Note: 10 ft./min. equals 3.048 m. /min.

Table IV: Appropriate personnel protective equipment for routine pharmaceutical manufacturing (40)

Protective Clothing	Non-sterile Manufacturing Areas	Sterile Manufacturing Areas
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Plant uniform or plant uniform with overalls for high-risk product and environment	Yes	Yes
Hair/beard coverings	Yes	Yes
Safety glasses	Yes	Yes
Dedicated shoes or shoe coverings	Yes	Yes
Gloves	Yes (if in direct product contact)	Yes
Face masks	Yes (if in direct product contact)	Yes
Enclosed respirators	Only if manufacturing high-potency, toxic drugs or infectious biological agents	Only if manufacturing high-potency, toxic drugs or infectious biological agents
Sterile cleanroom uniforms (coveralls), hoods, sleeves, goggles, face masks, and gloves	No	Yes, if in critical aseptic processing area

Table V: Capacity of SARS-CoV-2 to Replicate in Primate and Human Cell Lines

Cell Line	Cell Line Origin	SARS-CoV Replication	References
CHO	Chinese Hamster Ovary	Incompatible	(Kreil, 2020 Pers. Com.)
HEK293	Human Embryonic Cells	Incompatible	(Kreil, 2020 Pers. Com.)
HT1080	Human fibrosarcoma	Incompatible	(Kreil, 2020 Pers. Com.)
A549	Human Adeno carcinoma Cells	Incompatible	50
HUH	Human Liver Cells	Moderate	50
HEK293T	Human Embryonic Cells	Moderate	50
VERO	African Green Monkey Kidney Cells	High	50

Incompatible = No growth, No Cytopathic Effect (CPE); Moderate = Growth but no CPE; High = Growth and CPE

Figure Captions

Figure I: Direct and indirect risks that may result in pharmaceutical drug shortages

APPENDIX

HACCP Approach to Risk Assessment

A comprehensive risk assessment of the different parts of pharmaceutical supply chain may be found in Tables VI through XI. The four columns in each table address the input or activity, potential risk identification, assigned risk rating (low, moderate or high), existing critical process controls and recommended risk mitigations. The risk assessment model used is based on food-based HACCP principles that may be unfamiliar to some people working in the pharmaceutical industry (45). These represent the informed opinions of the authors with an emphasis on the risk assessment process and an attempt to capture all relevant aspects of the steps in the supply chain.

Table VI: Risk Assessment – Management of Human Resources during a COVID-19 Pandemic

Activity	Risk Identification	Risk Rating	Risk Mitigation/Critical Process Controls
Recruitment of new staff	Local; Regional; National; International	Low to Moderate	Remote interviews; Limit domestic and international travel; 14-day quarantine prior to starting work
Training new hires and existing employees	Lack of information; Issues not addressed in corporate policies and procedures	Moderate to High	GMP compliance; Coronavirus awareness training; Symptoms identification
Deployment of employees	Domestic; International	Moderate to High	Staff functions conducted from home; Restrictions on non-essential domestic and international travel; deferment of large staff meetings
Management and Supervision of Employees	Staff and line functions	Moderate to High	Illness recognition; Monitoring with thermal sensors; Universal wearing of non-medical facemasks on the job
Employee Attendance	Employees working sick; Loss of human resources; Inability to commute	Low	Flexibility in working hours; Stress importance of staying home when ill; Provide sickness benefits; Add company sponsored transportation when public transportation is unavailable

Table VII: Risk Assessment – Management of Manufacturing Materials during a COVID-19 Pandemic

Materials	Risk Identification	Risk Rating	Risk Mitigation/Critical Process Controls
Pharmaceutical Excipients	Excipients derived from plant, animal or mineral origin; Excipients of synthetic or semisynthetic origin	Low	Supplier awareness of potential COVID-19 risk; Standard duration of transit and hold times
Drug Substances	Drug substance of synthetic or semisynthetic origin	Low	Standard duration of transit and hold times
Packaging Components	Glass vials, stoppers and seals (Sterile products) Plastic container, heat induction seals and caps (Non-sterile products)	Low	Standard duration of transit and hold times; automation of component handling; washing, depyrogenation and sterilization (Sterile Products)
Labeling Materials	Labels and package inserts	Low	Reduce handling during label identification and reconciliation
Incoming Potable Water	Ground or surface water	Low	Communication with local water authority

Table VIII; Risk Assessment – Testing of Incoming pharmaceutical ingredients, packaging components, intermediates and finished products during a COVID-19 Pandemic

Materials-Sampling and Testing	Risk Identification	Risk Rating	Risk Mitigation/Critical Process Controls
Sampling of Incoming Materials	Human intervention; Limited environmental controls in warehouses	Moderate	Personnel Protective Equipment; sampling booths; labeling sampled containers
Transportation to the testing area	Transition through the facility	Low	Disinfection of the surface of containers, drums, shrink-wrap and pallets
Sample testing	Personnel handling	Low	Personnel Protective Equipment; limited access to testing area; environmental controls
Sample disposition	Disposal	Low	Controlled destruction of samples

Table IX: Risk Assessment – Management of Plant Utilities during a COVID-19 Pandemic

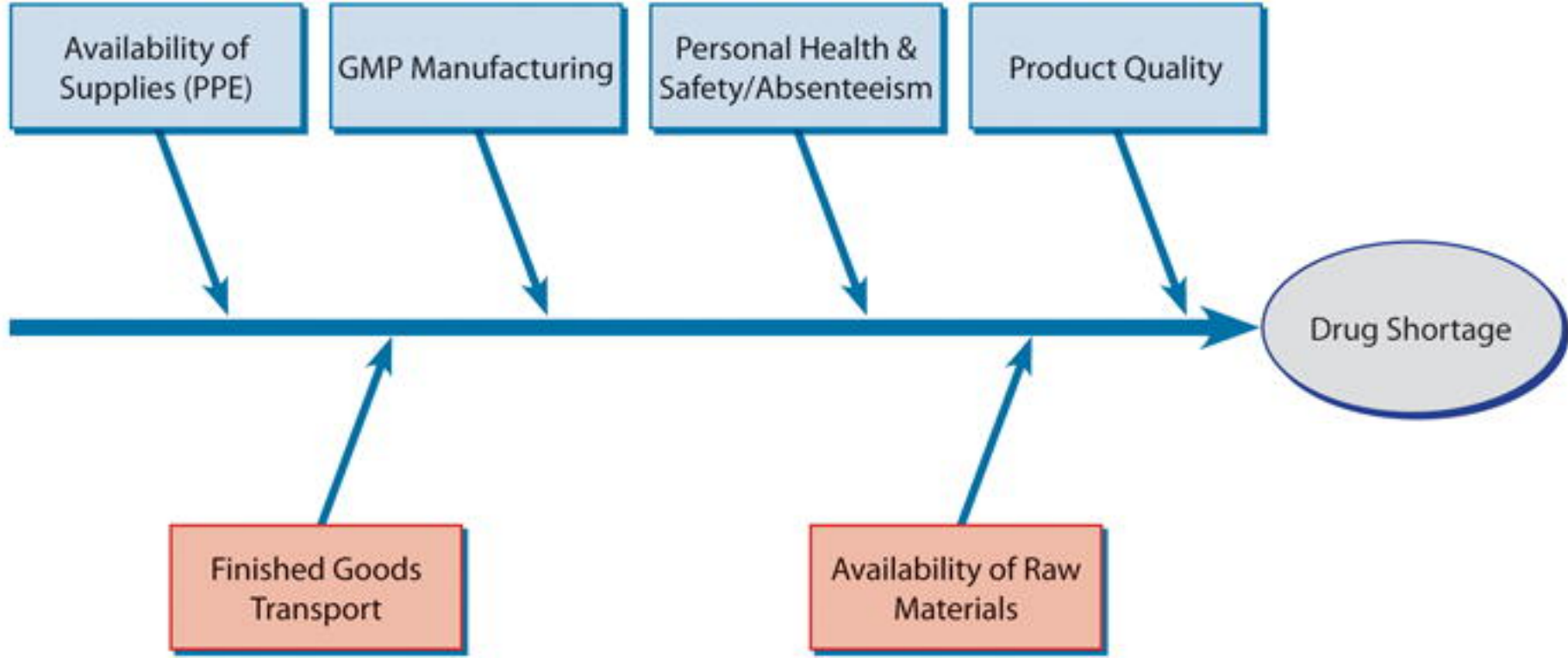
Materials – Plant Utilities	Risk Identification	Risk Rating	Risk Mitigation/Critical Process Controls
Pharmaceutical-grade Water	Incoming potable water	Low	Maintain existing microbial monitoring program
Pharmaceutical-grade Plant Air	Distribution lines and delivery nozzles	Low	Assure sanitary design
Compressed Gases	None	Low	Maintain existing microbial monitoring program
HVAC System	Poor temperature, humidity and air exchange, Re-circulation and lack of segregation	Low to Moderate	Reduced recirculation in more critical areas; Higher air change rates; High-room ultraviolet germicidal Irradiation
Domestic and Clean Steam	None	Low	None
Vacuum	Discharge	Low	Review vacuum discharge
Washing Facilities	Poor design and opportunities for cross-contamination	Low to Moderate	Access to detergents, hot water, and hand sanitizing agents; Segregation of clean and dirty materials
Waste and Sewage Disposal	Poor separation	Moderate	Backflow elimination; Segregation of clean and dirty materials

Table X: Risk Assessment - Representative Non-Sterile Drug Product (Compressed Tablet) during a COVID-19 Pandemic

Manufacturing Process	Risk Identification	Risk Rating	Risk Mitigation/Critical Process Controls
Incoming Material Sampling and Testing	Sampling is an invasive process	Moderate	Sampling booths; Personnel Protective Equipment (PPE)
Warehousing	Limited environmental control	Low	Improved environmental control
Ingredient Weighing	Weighing is an invasive process	Low to Moderate	Evaluate weighing booths and PPE
Excipient Size Reduction	Equipment cleaning	Low	Upgrade COP and CIP operations
Blending	Equipment cleaning	Low	Upgrade COP and CIP operations
Granulation – Dry Granulation - Wet	Equipment cleaning	Low	Upgrade COP and CIP operations
Compression	Equipment cleaning	Low	Upgrade COP and CIP operations
Bulk Tablet Storage	None	Low	None
Packaging and Labeling	Packaging operations are labor intensive	Low to Moderate	Evaluate HVAC Systems; Automation of component handling; PPE
Finished Goods Warehousing	Poor environmental control	Low	Improved environmental control
Shipping	Lack of chain of custody	Low	Dedicated carriers

Table XI: Risk Assessment - Representative Sterile Drug Products (Liquid-filled Stoppered Glass Vials) during a COVID-19 Pandemic

Manufacturing Process	Risk Identification	Risk Rating	Risk Mitigation/Critical Process Controls
Incoming Material Sampling and Testing	Sampling is an invasive process in a warehouse	Moderate	Sampling booths and Personnel Protective Equipment (PPE)
Warehousing	Limited environmental control	Low	Improved environmental control (IEC)
Ingredient Weighing	Weighing is a labor intensive process	Low to Moderate	Evaluate weighing booths and PPE
Bulk Solution Preparation	Solution preparation is a potentially invasive process	Low to Moderate	Use of Restricted Access Barrier Systems (RABS) and Isolators
Packaging Component Preparation	Component loading and unloading is a potentially invasive process	Low	Automation of component handling; Depyrogenation and sterilization of vials and stoppers
Sterile Filtration and Aseptic Filling, and Sealing	Aseptic processing is a potentially invasive process	Low	Use of RABS and Isolators
Visual Inspection	Inspection is an invasive process	Low	Handling automation; IEC; PPE
Packaging and Labeling	Packaging is an invasive process	Low	Handling automation; IEC; PPE



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