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A REVIEW OF CONTAMINATION CONTROL IN PHARMACEUTICAL INDUSTRY IN THE CURRENT SARS-COV-2 PANDEMIC CONTEXT

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Abstract

The objective of this paper is to assess whether the contamination control measures already being applied in the pharmaceutical industrial production are efficient enough in the context of a viral pandemic, such as the SARS-CoV-2 pandemic of 2020-2021. The questions that must be asked are linked to the efficacy of already existing virucides against the newly discovered viral strand and whether there is a need for supplementary precautions in regards with the workers that have direct contact with the finished product or operate the machines that package the finished goods. The discussion will revolve around the efficacy of current protocols of disinfection, the need for workers' continuous and rigorous training, and the transparency in which quality control must be implemented, as to ensure the public's trust in the industrial process.

Key words: *SARS-CoV-2 pandemic, protocols of disinfection, pharmaceutical industrial production.*

INTRODUCTION

The importance of discussing the safety of industrially obtained goods in the context of a viral pandemic is immediate, especially since the SARS-CoV-2 pandemic still has a great deal or resonance at a global scale. Moreover, the repercussions of this pandemic are yet to be felt in the coming months. The pharmaceutical industry has always been harshly conditioned by the law and in regards to protocols that need to be followed for a rigorous contamination and quality control and assurance, these laws are quite explicit – the European Pharmacopoeia would be a good reference (Council of Europe, 2021). The FMEA (Failure Mode and Effects Analysis) systems of all pharmaceutical production facilities have a great contribution to not only delivering safe products to the patients, but also, in ensuring the protection of their own employees (Greulich & Hardy, 2009; American Bureau of Shipping, 2015). However, in the previously mentioned context of a viral pandemic the question that arises is whether all these measures are enough in order to ensure the stop of the viral spread. Even though the world has experienced previous challenges with similar viruses, such as SARS-CoV and MERS-CoV, the novel SARS-CoV-2 has been proven to be a lot more contagious, thus making its spread, a lot harder to control (Wang et al., 2020) causing this pandemic to become an unprecedented worldwide situation. In the case of MERS-CoV, for example, even though the mortality rate was considerably higher than for SARS-CoV-2 (36% for MERS-CoV and 2.84% for SARS-CoV-2), the transmission did not occur at such intensity, most of the world never really having to deal with it (Sun et al., 2020; Liang et al., 2018).

It is important to understand that most manufacturers do have strict hygiene norms that are meant to protect employees from accidental poisonings and prolonged exposure to chemicals and to ensure that no contamination becomes the products, neither within their production, nor upon their packaging (Vijay et al., 2020).

Another aspect that deserves attention is the fact that some studies have demonstrated that the new Coronavirus can remain viable for quite a relevant period of time on various surfaces and in wastewater, thus it is transmission does not necessary have to be immediate, from infected human to a healthy human via droplet route (Wiktorczyk-Kapische et al., 2021).

It is clear that the purity standards that all the products being manufactured in a pharmaceutical facility are being subjected to,

render a very low possibility on the finished good being a SARS-CoV-2 transmission vector. However, in order to prevent a viral outbreak within the factory, the staff must comply not only with the usual hygiene protocol, but to understand the implications of not respecting it, since even the PPE (Personal Protection Equipment) can carry a viral load for quite some time if not properly disinfected, as demonstrated on single-use masks, nitrile gloves, plastic and more by Kasloff et al. (2021).

The objective of this review is to assess the risk that is linked to the SARS-CoV-2 virus paths of transmission and hopefully provide manufacturers with much more compiled, reliable information, so that they may protect not only their businesses but also the very important work force that effectively conducts the activity on site and whose presence is impetuous.

MATERIALS AND METHODS

This review was based strictly on theoretical research. The materials used are represented by scientific publications of researchers and authorities from around the world which were compared in order to reach a common ground and draw the necessary conclusions in order to formulate some recommendations that are relevant to the pharmaceutical production in the context of the SARS-CoV-2 pandemic.

RESULTS AND DISCUSSIONS

LEGAL SURROUNDINGS

After scrutinizing the legal aspects presented on different official EU websites, such as www.ema.europa.eu, as well as US websites, such as www.osha.gov it is clear that the authorities have not deemed necessary to enforce any special protocols, in regards to the SARS-CoV-2 pandemic, other than minimizing the risk of spreading the virus through physical contact, which would have been needed in order to obtain different kinds of authorisations. Therefore, existing documents may have received a validity extension, while the process of obtaining new such documents has either been postponed to a safer ulterior period or has been enabled via electronic online methods (EMA, 2020).

It is clear that the production process in itself, especially when it comes to pharmaceuticals is very well regulated and clean, including from a microbiological standpoint.

The manufacturers therefore need to be responsible and have been allowed to carry on with their very important activities, provided that they prevent outbreaks. In order to do such thing each manufacturer has been given a free hand in managing their own plants.

Of course, the WHO (World Health Organization) recommendations are a very helpful start point (WHO, 2021), but if one is to ask more than one producer what steps they have been taking in stopping the spread of the virus inside their facilities, one may notice that the strategies can be very different from one another.

RECOMMENDATIONS ON MANAGING ESSENTIAL WORKERS

In the United States of America, the CDC (Center for Disease Control) has issued a number of recommendations from OSHA (Occupational Safety and Health Administration) with the intention of helping the manufacturers that operate in the essential industries better manage the pandemic situation (OSHA, 2021). Amongst other, recommendations such as wearing a mask, practicing social distancing and disinfection of shared working spaces are indeed a must. However, any employee that has had recent contact with another person that has been tested positive should not attend work for 5 to 6 days (OSHA, 2021) even if the employee does not have any symptoms, as it has been demonstrated that the incubation period for the virus can vary. The pool average incubation period for SARS-CoV-2 discovered through a review which includes numerous peer reviewed studies was about 6 days (Wassie et al., 2020). Another research showed that even though the rate of transmission for asymptomatic carriers was much lower than for symptomatic carriers, there is still a hard to ignore risk for the spread of the disease (Liu et al., 2020).

Therefore, the working space should be redesigned as to help in respecting the

recommended social distance between workers, the work stations should be thoroughly disinfected before each shift begins and the facility should be well ventilated in order to minimize spread via droplets (ECDC, 2020). There is extended research demonstrating the viability of the virus on different types of materials, such as: cardboard (24 hours), steel and plastics (2-3 days); and also in aerosols - 3-4 hours (Aghalari et al., 2021). This piece of information underlines the extreme necessity of strict disinfection protocols and of air ventilation in the workplace, even if the effective infection of an individual can only occur when the virus reaches some type of mucus membranes (nose, eyes, mouth) as sustained by Fernández-Raga et al. (2020).

The personnel should always have at hand some kind of efficient disinfectant and should be instructed to use it as often as possible during their shift. Substances that have proven themselves efficient against the COVID-19 virus include: >70% concentration alcohol based solutions, 0.1% sodium hypochlorite, 0.5% hydrogen peroxide (Wiktorczyk-Kapischke et al., 2021). The National Institute of Technology and Evaluation (NITE), in a study conducted in 2020 have presented other substances that have been proven effective in neutralizing the virus such as: sodium linear alkylbenzene sulfonates (0.1% or more), alkyl glycosides (0.1% or higher), alkyldimethylamine oxide (0.05% or higher), benzalkonium chloride (0.05% or higher), benzethonium chloride (0.05% or higher), dialkyldimethylammonium chloride (0.01% or higher), polyoxyethylene alkyl ether (0.2% or higher), potassium soap (0.24% or higher), sodium soap (0.22% or higher). It should be emphasized that a recommendable exposure time of the possibly infected surface to the disinfectant is at least 30 seconds (Rabenau et al., 2004; Kampf et al., 2020). Even though SARS-CoV-2 is very adaptable to a wide range of pH values (3-10), at room temperature, it is also highly susceptible to standard disinfection protocols (Chin et al., 2020).

Also, any objects or pieces of equipment that are not individual, but shared, such as phones, keyboards, mouses, barcode scanners etc., present a higher risk to become a transmission path for the disease and therefore it is strongly recommended that they be disinfected after each use (Bloise et al., 2020).

Another important issue that needs to be addressed is the traceability of any confirmed cases within the facility. For this, the employer must not only inform all of their employees of the known symptoms of the disease, but also to ensure that they trace every person that may have come in contact with the infected person and advise them to remain at home for the recommended time period, and if possible test themselves. Any worker that presents any kind of symptoms either when presenting at the facility to start their shift, or developing them during their shift should be sent home immediately along with any other worker that may have been put at risk (OSHA, 2021). To be noticed that the planning of the shifts should also be made in such a way that allows the employer to be able to continue the production process even if some of the workers have to be sent home, by each department. COVID-19 symptoms include: coughing, dyspnoea, fever, anosmia, headaches and fatigue; and this information should be on display at all times. (Antonelli et al., 2021).

If any employees have been traveling to a red or dark red zone, they should be advised to undergo testing or self-isolate, though traveling is not recommended unless there is an immediate need for it (Council of the EU, 2021).

Even though there have previously been certain confrontations with viral pandemics (6 influenza pandemics between 1889 and 2009 for example), since the SARS-CoV-2 pandemic is present on a global scale and the modern world we live in is the perfect environment for a much faster spread rate, some manufacturers around the world have never been involved in the efforts to stop such a spread as per the present scenario (Monto & Webster, 2013).

A comparison between WHO recommendations, OSHA recommendations and CDC recommendations can be observed in Table 1.

By this comparison, one can observe that OSHA (OSHA, 2021) did concentrate on workplace aspects, while WHO (WHO, 2021) and CDC (CDC, 2021) have a more general approach, with recommendations that may suit the general public in all possible endeavours.

While the general approach seems insufficient, it does represent a good backbone in creating an efficient plan to combat the spread of the virus in the workplace.

Table 1. Comparison between OSHA (Occupational Safety and Health Administration), WHO (World Health Organization), and CDC (Center for Disease Control) recommendations on managing essential workers

Recommendations	(OSHA, 2021)	(WHO, 2021)	(CDC, 2021)
Wearing a mask	✓	✓	✓
Practicing social distancing	✓	✓	✓
Frequent hand disinfection / washing	✓	✓	✓
Frequent disinfection and cleaning of high-touch surfaces	✓	✓	✓
Telework when possible, and avoidance of crowded spaces	✓	✓	
Hazard assessments (identifying when and where workers may become infected)	✓		
Identification of a combination of measures which will limit viral spread	✓		
Supportive policies for high-risk employees	✓		
Trainings for a better understanding of the SARS-CoV-2 symptomatology	✓	✓	
Isolation of employees who become symptomatic at work	✓		
Guidance on screening and testing	✓	✓	
Enhanced cleaning after a SARS-CoV-2 infected person has been in the facility	✓		
Vaccination is advisable	✓	✓	✓

VIABILITY OF SARS-CoV-2 ON INANIMATE SURFACES

Doremalen et al. (2020), have conducted a study in which, maintaining a room temperature (21°C-25°C) and a 40% RH (relative humidity), have tested the viability of SARS-CoV-2 on different types of surfaces and in aerosols, finding that the half-life of the virus was approximately 5.6 hours on stainless steel and 6.8 hours on plastics. Wiktorczyk-Kapischke et al. (2021) have comparatively assessed the viability of SARS-CoV-2 and other related viruses, effectively demonstrating that SARS-CoV-2 is highly sensitive to temperature, it's persistence on different surfaces being greatly diminished by increasing the temperature values. Combined data is presented in Figure 1 (Ridell et al., 2020; Doremalen et al., 2020; Chin et al., 2020).

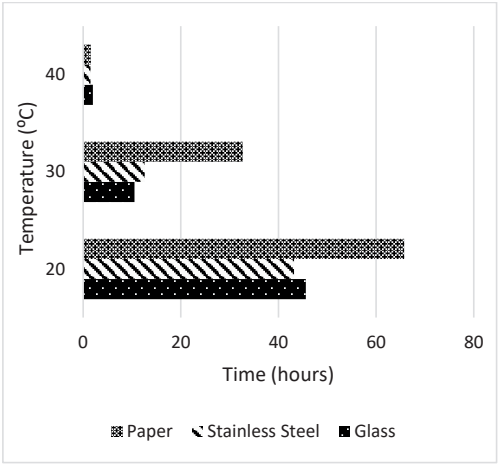

Figure 1. Persistence of SARS-CoV-2 on relevant surfaces (paper, stainless steel and glass), in function of time (hours) and temperature (°C)

WASTEWATER AS A POSSIBLE TRANSMISSION PATH

As in any kind of industrial production facility, water that is used in pharmaceutical production is of the greatest purity (Strade et al., 2020), including at a microbiological level and the water that employees use to wash their hands for example does not come into contact with any of the ingredients used in production, as all production sites have most certainly designed different water flow systems, depending on its use.

However, even if this design does prevent any contamination of the product within the production process itself, it has been demonstrated that the SARS-CoV-2 virus can retain viability within hospital wastewater, and

therefore it is possible for it to remain viable in at least one type of wastewater that the site produces (Achack et al., 2020). This not only implies how imperative it is for the staff to respect the hygiene implemented norms when visiting the restrooms or any other common areas, but also the need for a responsible disinfection of the potentially infected wastewater. Since hydrogen peroxide and chlorine based substances have been proven effective against the virus, perhaps such a treatment would be recommended for the facilities (Chen et al.,2014; Achack et al.,2020).

CONCLUSIONS

Never before has the science of epidemiology has been more needed than in the era of transportation in which we currently live and never before has it been more important for leaders and individuals to understand what combat strategies to adopt, in relation to the area they live in (Widdowson & Monto, 2013).
All of the recommendations made in the present review were made with the intention of establishing a general protocol which should be applicable to all industrial production sites, a general protocol that is unprecedented, due to the newly discovered relation between the concept of a viral pandemic and the role that industrial manufacturers have to play in a global scale sanitary crisis. The pre-SARS-CoV-2 pandemic contamination control protocols are efficient up to a certain levels and supplementary measures are needed in order to ensure the protection of employees.
To conclude this review, the final recommendations upon efficiently managing a pharmaceutical production site in the context of the SARS-CoV-2 pandemic may revolve around the need for transparency and ethical decisions. All points considered, a thorough training of the employees and recurrent informational campaigns should run through the facility, the management should redesign the shifts and ensure the protection of their employees within their facilities produce. Human contact with the finished goods should be limited to a maximum if not even completely eliminated from any production or packaging process. A skilful combination of the presented data should ensure a healthy continuation of production in the safest possible environment.

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