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Stringent isolator technology when handling highly pathogenic BSL-4 materials

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Abbreviations: HEPA, high efficiency particulate air (filter); ULPA, ultra low particulate air (filter)

Introduction

The recent Covid 19 pandemic has shown the importance of the protection versus high pathogenic microorganism's viruses and bacteria. The research work on highly contaminating virus leads to the use of a "bunker" type of lab (P4 Lab) to allow researchers and employees to be protected and to avoid cross-contaminations between the studied microorganisms. At the date of today thanks to around the 40 P4 labs implemented worldwide with success we have been able to work, discover and fight against dangerous pathogenic agents like Marburg, Ebola and now Covid 19. The P4 lab technology uses means of barriers versus airborne contaminations, human contaminations and components contaminations during the stringent procedures of research, discovery and production.[1] The purpose of this very article is not to go beyond the P4 technology but using the same separation techniques to propose an alternative making the availability easier for the operators time wise and technologically wise.

Where from is the danger at biosafety level (BSL) 4?

WHO has defined four biosafety levels. Each level has specific controls for containment of microbes and biological agents.[2] The primary risks that determine levels of containment are infectivity, severity of disease, transmissibility, and the nature of the work conducted. Origin of the microbe, or the agent in question, and the route of exposure are also important.

Each biosafety level has its own specific containment controls that are required for the following:

a. Laboratory practices

b. Safety equipment

c. Facility construction

BSL-4 laboratories have the following containment requirements:

a. Personnel are required to change clothing before entering, shower upon exiting

b. Decontamination of all materials before exiting

Personnel must wear appropriate personal protective equipment from prior BSL levels, as well as a full body, air-supplied, positive pressure suit.

A Class III biological safety cabinet which has identical features as a closed isolator in negative pressure.[2]

A BSL-4 laboratory is extremely isolated, in negative pressure- often located in a separate building or in an isolated and restricted zone of the building. The laboratory also features a dedicated supply and exhausts air, as well as protected vacuum lines and reproducible decontamination systems. What alternative with the same separation technologies, knowing that each piece of technology has to be validated prior and after use.

The environment physical barrier

A controlled area in which operators are working with pathogens elements must be a physical barrier in which the level of accepted leak is defined, measured and validated. The ISO 10648-2 gives values and the class 2 or 3 with a negative pressure versus the immediate environment at minus 15 Pa is enough. A controlled cascade of 3 pressures between the working zone, the personnel and components gives a protection during the operations. The hourly air renewal in each separated volume is between 10 and 20, temperature is between 20-22°C and relative humidity between 50 to 60%. This environment is defined elsewhere as a "ballroom concept"[3] which is for the operator a comfort for working and walking. The clothing according to ISO14644-5 (Annex B) is a Class C or D type meaning an access or exit to the working area within a maximum of 10 minutes.

The physical barrier of the isolator

The alternative to the "Wuhan type of P4" (seen also in the movie Outbreak) is the use of "closed isolator" as defined in the Bio-pharmaceutical industry:[4] "Excluded external contamination from the isolator's interior by transfer material via aseptic connections to auxiliary equipment rather than using openings to the surrounding environment. Closed systems remain sealed throughout operations." The Bio-pharmaceutical industry uses routinely isolators since the beginning of the 90s either for aseptic process or toxic process or both.[5,10] The proposed isolator for this very application is made from a transparent flexible film with the same thickness than the suit of the operator in a conventional P4 lab. It is ready to use, sterile, and single use. As it works in a negative pressure, it is fixed on an outside frame to avoid it to collapse. The negative pressure airborne protection from viable and non viable particles is assured through a

double HEPA/ULPA inlet filtration and a double outlet HEPA/ULPA filtration. These filters are of the same nature and technology as the ones used in Biosafety Cabinet and also for the air filtration of the P4 Lab. The usual size of the proposed one operator isolator is 1200 (L) X 600 (W) X 700 (H) mm. Its design sophistication depends upon the application, it can include fluid connectors, cable connectors, pockets for an external incubation…Made from a flexible film it has a bespoke shape.

The stringent transfer system

To transfer safely contaminated elements from one isolator to another one with a complete protection of environment and operators, the isolators are equipped with DPTE®/RTP systems (Figure 1) which allow a bidirectional protection for the operators/environment and from the pathogenic elements and toxic components. Containers of this RTP system are used as entrance/exit ways and to store and to waste during the operations (Figure 2). This transfer system which has first be patented in 1966 for transferring safely radioactive waste is routinely and worldwide used for sterile and toxic transfers in the Bio-pharmaceutical industry.[6,7]

In fact the proposed isolator here is a Beta RTP system with a configuration of a disposable negative pressure isolator. The possible RTP diameters are 105, 190, 270 and 350mm. The isolator is gamma sterilized as a medical device and introduced in the room through a H_2O_2 lock chamber, then loaded with the needed components through its Beta RTP connection before to be connected to the Alpha RTP mounted on the wall of the room to transfer safely the pathogenic material from the outside (Figure 2). This pathogenic material is then kept inside the isolator for the different handlings to be performed. Ideally it's a Wifi paperless environment with outside of the isolator camera/magnifier/screen to control the status of the microorganisms. The goal is to reach a "never touch" situation. At the end of its use the disposable isolator goes through a two-door autoclave or equivalent to inactivate the biological materials before to be incinerated outside (Figure 2).

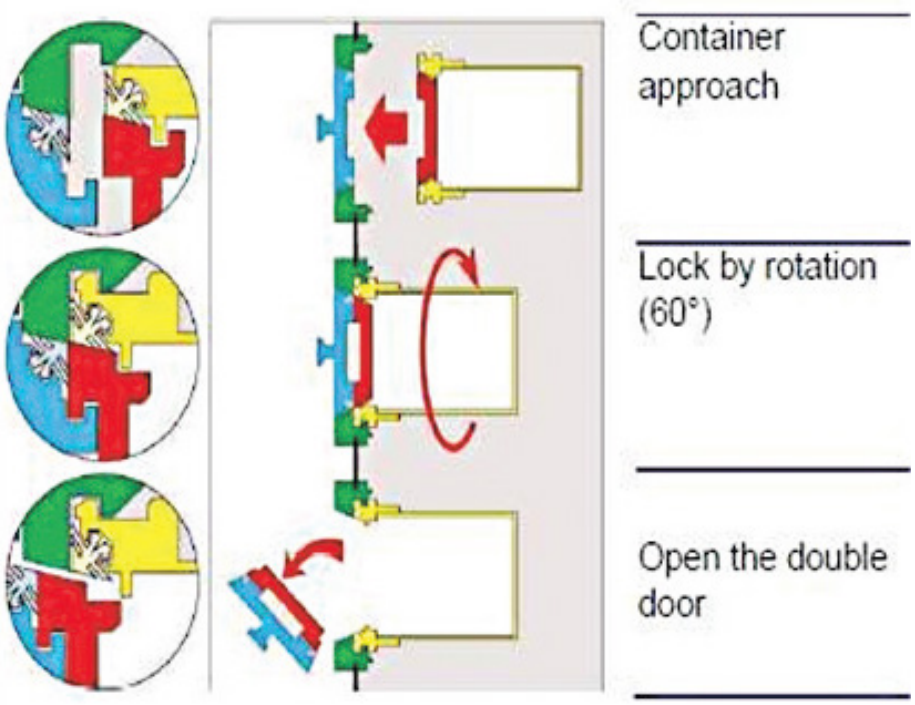

Figure 1 RTP transfer (from La Calhène).

The centrifuge dilemma

Centrifugation is a source of aerosols from the centrifuged liquid. When working with pathogenic materials it's usual to cover the rotors or to isolate the centrifuge. The proposed alternative here is to use RTP container as a rotor to assume a double role of airtightness and safe transfer (Figure 3) avoiding any modification on the centrifuge. A service isolator allows the necessary protected RTP transfer connections from vertical to horizontal in relation with the centrifugation (Figure 2).

The operator comfort

The use of isolators gets rid of a full suit with the risky procedures of gowning/cleaning/de-gowning. The operator has the comfort of a conventional Class C or D clothing. The access in the isolator is done with the isolator gloves offering a choice of materials, sizes and thicknesses and when necessary a glove interchange without breaking the airtightness.[8]

The protection of the outside

In the recent events at Wuhan there was a discussion and an audit to demonstrate that the source of the spreading of the virus responsible of the Covid 19 was not due to a mishandling in the Wuhan P4 lab. Here, all the exiting from the lab goes through a biological inactivation in a two-door autoclave before an incineration outside. The pathogenic materials are enclosed between RTP connections and two-door autoclave. The whole lab management (people/equipment/components/pathogens) follows protocols under a Data Integrity umbrella.[9]

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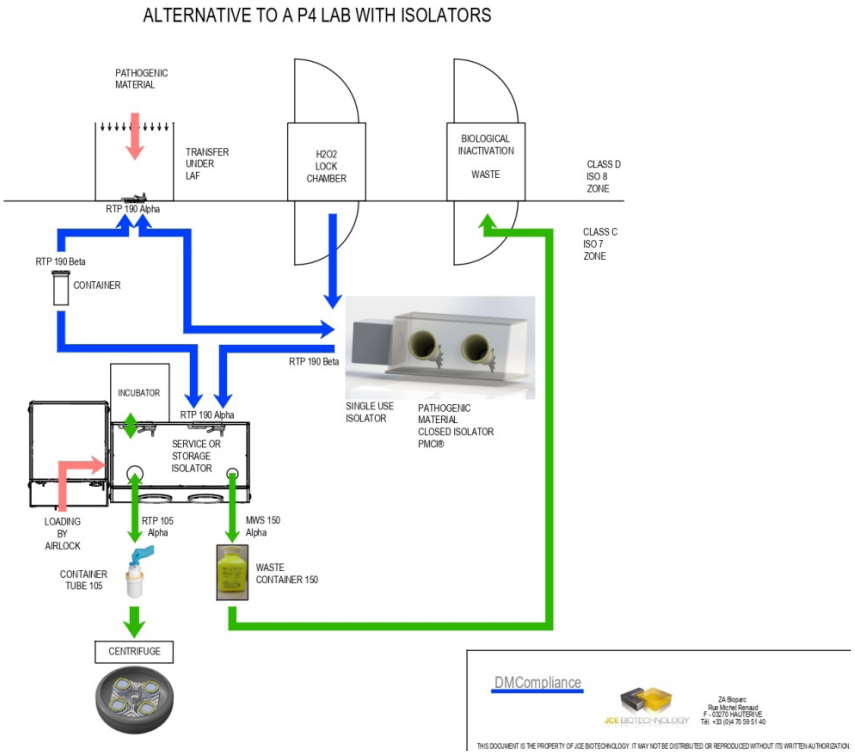

Figure 2

Figure 3 Vertical RTP transfer for rotor.

Conclusion for a safe routine

The schematic of a lab to handle BSL 4 pathogens using isolator/RTP technologies (Figure 2) shows an easier routine within a maximum safety. Nothing new but an addition of isolator/RTP validated techniques to fit within an ever risky BSL 4 handling. "Bunker" or "Ballroom" both brings the necessary segregation to upgrade the knowledge regarding actual and future pandemics.

Acknowledgments

Figure 3 and Figure 2 are published by courtesy of JCE Biotechnology.

Conflicts of interest

Author declares that there is no conflict of interest.

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