



COVID 19 – Facility Risk Assessment

- *PDA Israel*
- *April 26th 2022*

- *Gil Zomber*
- *Gil Pharma*

		Risk Vs. Mitigation Matrix			
		Very Prepared to Mitigate COVID-19 Impacts (0-100)	Somewhat Prepared to Mitigate COVID-19 Impacts (10-50)	Somewhat Unprepared to Mitigate COVID-19 Impacts (25-50)	Very Unprepared to Mitigate COVID-19 Impacts (50-100)
KEY					
Very Low	Overall risk of transmission and further spread of COVID-19 is considered very low				
Low	Overall risk is low , however recommend checking if mitigation measures can be strengthened				
Moderate	Overall risk is moderate , recommend significant efforts to improve mitigation measures or reduce risk of transmission should be made				
High	Overall risk of transmission and further spread of COVID-19 is considered high				
Very High	Overall risk of transmission and further spread of COVID-19 is considered very high				
Total Risk Score					
0 (very low risk)		Very Low	Very Low	Low	Moderate
1 (low risk)		Very Low	Low	Low	Moderate
2 (moderate risk)		Low	Low	Moderate	Very High
3 (high risk)		Moderate	Moderate	Very High	Very High
4 (very high risk)		Very High	Very High	Very High	Very High

Instructor

- Dr. Gil Zomber, freelance quality consultant and Senior Associate in the Compliance Practice at Lachman Consultants.
- Quality Systems, Internal and external audits and mock inspections, GMP audits of CMO's and supplier audits, support in preparation for and during FDA inspections.
- Member of the Executive Committee Members of the Israel Chapter of PDA.
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COVID 19 Risks

Shortage in raw materials,
packaging material and process aids

Management of human resources

Supplier's audits

Responding to COVID-19 infection in
employees

Supply chain risk categories

Sample Risk Category	Illustrative Risk Events
Supplier Risks	• Supplier financial crisis • Supplier regulation non-compliance • Supplier IT systems disruption • Supplier counterfeit parts
Environmental Risks	• Natural disasters (e.g. earthquake, flood) • Pandemic • Terrorism • Industrial accidents
Product Risks	• Raw material price fluctuation • Currency fluctuation • Product development delays • Product quality impact
Process Risks	• Equipment breakdown • Under/over capacity • Material Scarcity
Transportation Risks	• Air/sea port disruption • Freight capacity shortage • Inter-partner communication break down

Table 5.1: Supply Chain Risk Categories (Source: Supply Chain Resilience Model. Used v PricewaterhouseCoopers.)

סגירת אספקת חומרי גלם מהודו במשך כחודש

The government, on March 3, restricted the exports of **26 API and formulations, including paracetamol and vitamins B1, B6 and B12 in order to ensure there is no shortage of drugs** in India due to the lockdown in China's Hubei's province, the epicentre of the coronavirus outbreak, and a major source of these raw materials.

Tinidazole, metronidazole, acyclovir, progesterone, chloramphenicol, erythromycin salts, neomycin, clindamycin salts and ornidazole were the other APIs whose exports are now restricted. According to reports, the restrictions were imposed because India's manufacturers rely heavily on imports of their APIs from China. As a result of the lockdowns and closures, slowed production of APIs by the latter resulted in less availability and higher costs for the materials required for generics production. Duffy said the primary reason behind the export restrictions was to prevent domestic shortages in India in the long-term.



Govt frees exports of all APIs, formulations except paracetamol – 6 April 2020

In a Bind

Most pharma ingredient production concentrated in Hubei province



Capital Wuhan is the epicentre of coronavirus outbreak

30-40 units of basic chemicals, API & intermediates in Hubei supply products to India

Other centres **Zhejiang and Jiangsu** are close to Wuhan

For some APIs, dependence on China is over **80-90%**

India imported ₹**17,400 crore** worth of APIs from China in FY19: Pharmexcil

סגירה של מפעלים בסין לחודשיים

In Hubei province, where COVID-19 emerged, there are 44 companies that are FDA-approved and/or meet EU standards and manufacture APIs or supply chemical ingredients to API manufacturers. Most of these companies have been shut down since January 24, 2020

China factories re-open with the support of the government-

Government's supports are effectively. According to China's Ministry of Industry and Information Technology, as of March 28, the resumption of work rate for larger industrial enterprises was 98.6 percent. The return rate of workers stood at 89.9percent.

The Effects of COVID Lockdowns on Transportation Within China

By David Collins III, 20 April 2022



Much of the news coverage of COVID lockdowns in China focuses on its effects on the international supply chain and the scarcity of certain goods, especially electronics. While that is understandable, it is only a part of the larger story. The more important consideration is how the lockdowns have affected businesses within China, not just with workers unable to go to work, but the trucking industry unable to

move materials between locations. One of China's great strengths is its vast and interconnected supply chain. The selective lockdowns in various cities and municipalities create a difficult and unpredictable situation for any company working in China.



More Than 11.5 Billion Shots Given: Covid-19 Tracker

In the U.S., 572 million doses have been administered

Updated: April 23, 2022, 3:11 PM GMT+3



- Medical vials are made of Type I borosilicate glass.
- In the short term, it seems that the current shortage is due to slow growth of the vials manufacturing industry combined with an unexpected surge in demand. The glass-vial industry is heavily capital-intensive due to the cost to acquire the equipment. Another consideration: The equipment consumes a lot of energy — the furnace used to melt the sand, for example, runs at close to 2,000 degrees when no vials are being made. Additionally, special requirements like precision details, manufacturing process control, level and intensity of quality checks lead to additional cost.
- In the long term, experts say the shortage will be driven by the lack of a core ingredient: sand. Though there may be plenty of sand on the planet, not all of it is usable for glass vials. The type suitable for making Type I borosilicate glass is silica sand. Containing large amounts of silicon dioxide (SiO_2), the resulting glass is chemically inert. As the concentration of SiO_2 increases, so does the clarity and strength of the resulting glass. Silica sand is also used in construction (concrete, shingles and mortar) and in the technology industry (computer chips).





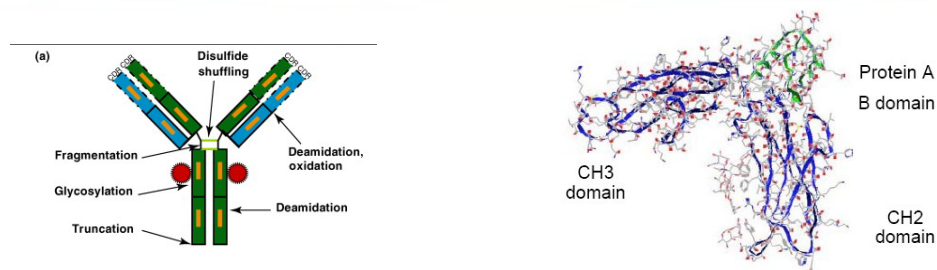
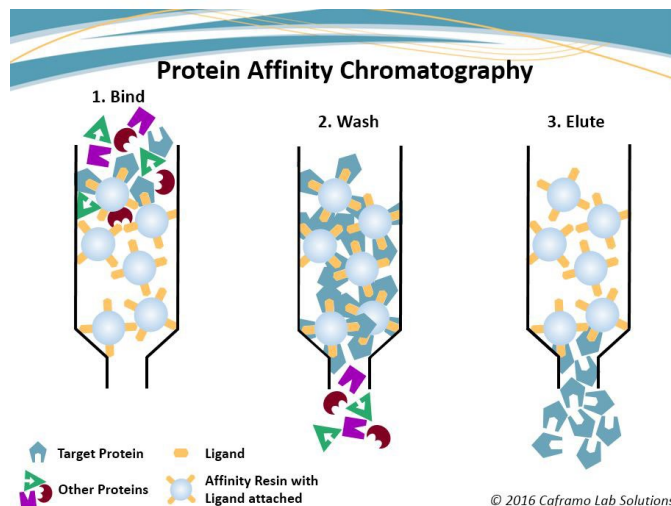
Increases in Manufacturing Capacity Target Vial and Syringe Shortages

- Recent investments in manufacturing capacity include Corning, BD, and SiO₂. In June 2020, Corning was awarded \$204 million by the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the US Department of Health and Human Services, through its partnership with the Department of Defense's Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense and Army Contracting Command. Under the contract, Corning was tasked with expanding its domestic manufacturing capacity for its glass vials for COVID-19 vaccines

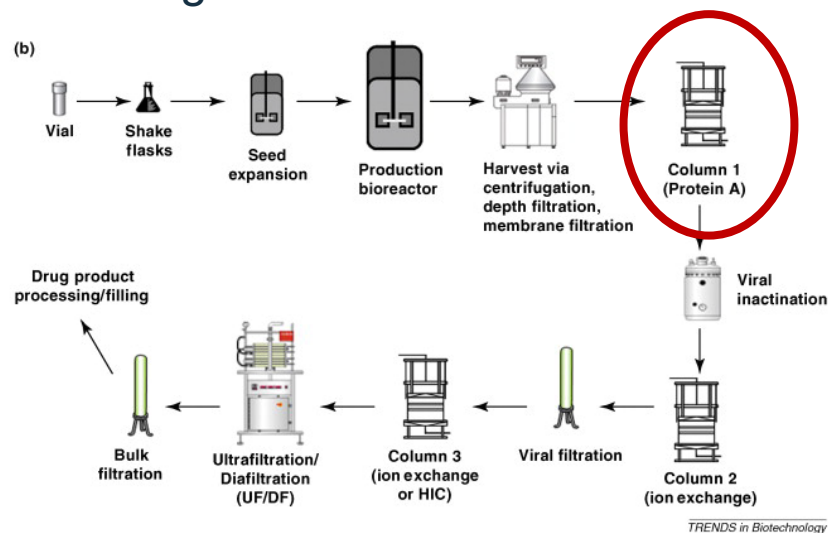
There should be:

- Regularly updated systematic lists in place which indicates the criticality of starting material or component and related contingency measure
- Routinely monitored actions for remediation of critical materials
- The results should be assessed as part of on – going quality risk assessment and crises plan
- For critical sole-sourced materials there should be suitable contingency planes in place to avoid drug shortages.

Shortage in protein A resin



High levels of purification can be achieved through the use of protein A affinity resins. This is because antibodies selectively bind protein A ligands with the resins.



Shortage in protein A resin

- 12,000- 15,000\$ L
- For 120L (commercial 2000L fermenter) ~ 1.5M \$
- Lead time – 1 year!
- Chromatography is an essential step in the purification of monoclonal antibodies (mAbs). Over the past decade, there has been a tremendous increase in the demand for monoclonal antibodies in oncology and several other therapeutic areas, including neurological, autoimmune, and inflammatory disorders. As a result, almost all major pharmaceutical companies are focusing on the R&D of therapeutic antibodies.
- The outbreak of COVID-19 accelerated the sales of protein A resins as development of monoclonal antibodies for the treatment of virus increased.
- Researchers are optimistic that monoclonal antibodies could help prevent and treat early infections of COVID-19. Several monoclonal antibodies that are licensed or in development for other diseases are in clinical trials for COVID-19

מחסור בעובדים עקב:

סגרים

בידודים (עובד, בן משפחה)

הדבקות במחלה (עובד, בן משפחה)

עבודה מרחוק- לא ישימה לעובדי ייצור ועובדי מעבדה

Pfizer, Moderna and Alnylam flag pharma labor shortage in Massachusetts—and the people bottleneck doesn't stop there

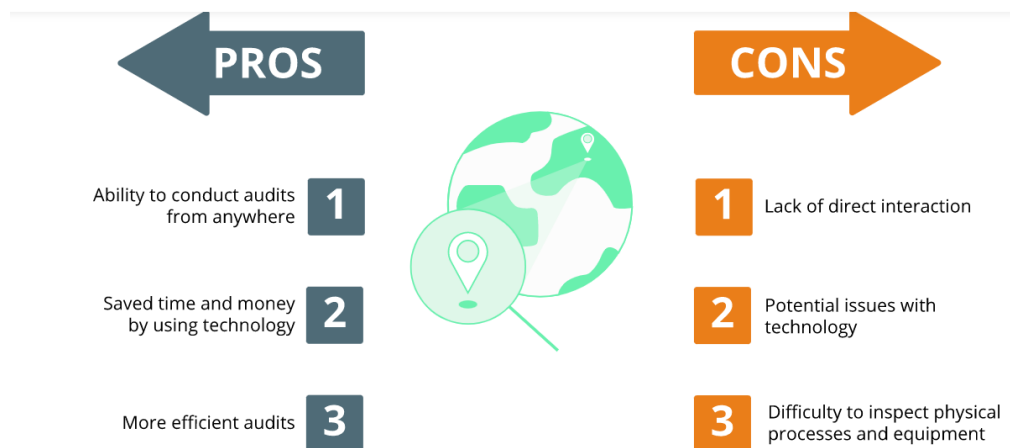


Suppliers' audits

- Planned supplier audits were postponed during the COVID-19 pandemic

Current solutions:

- Paper audits/ questionnaire
- Remote audits
- Outsourced audits



Remote Audit Best Practices



Contains Nonbinding Recommendations

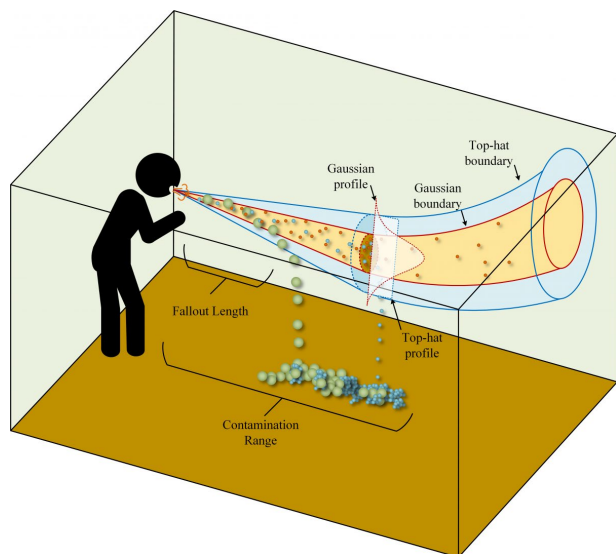
Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing

Guidance for Industry

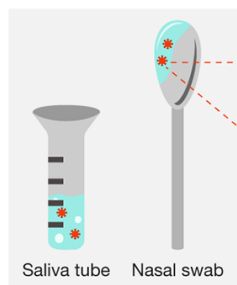
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Veterinary Medicine

June 2020

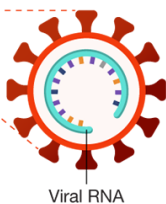
Risk Assessment for the potential viral contamination caused by sick operator



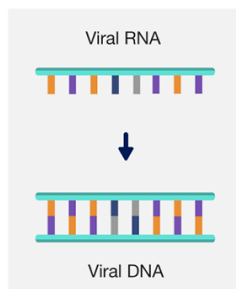
Sample collection



SARS-CoV-2 virus



Reverse transcription



אחריות אישית

- The preliminary results of recent research indicate the following regarding SARS-CoV-2:
- It is stable for several hours to days in aerosols and on surfaces
- The incubation period of SARS-CoV-2 and other human coronaviruses such as SARSCoV-1 and MERS-CoV is 2 to 14 days

For drug products, 21 CFR 211.28(d), “**Personnel responsibilities**,” requires that:

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 responsibilities

Persons whose presence can affect adversely the safety and purity of a product shall be excluded from the room where the manufacture of a product is in progress.

אדם שנוכחתו עלולה להשפיע
על בטיחות וטוהר המוצר לא
ישהה בחדר שבו מיוצר מוצר

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- To help prevent transmission among employees and contamination of drugs/materials by a COVID-19-infected employee engaged in drug manufacturing at the workplace, drug manufacturers should:
- Clean and sanitize non production areas (such as offices, elevators, break rooms, changing rooms, and restrooms) more frequently.

ניקוי וסניטציה של אזורים שאינם ייצור
כגון משרדים, מעליות, חדרי מנוחה, מלתחות, שירותים



Update existing procedures to institute more frequent cleaning, sanitization, and/or sterilization of surfaces in the production areas, particularly surfaces that are contacted frequently, such as door handles, equipment latches, bench/counter tops, and control panels. Special attention should be paid to sanitizing/sterilizing equipment and product contact surfaces.

מומלץ לעדכן פרוצדורות נקיון לנקיונות וסניטציה בתדירות גבוהה יותר של אזורי ייצור, בדגש על משטחים שנוגעים בהם בתדירות גבוהה, כגון:

ידיות של דלתות
ידיות של מכשור
לוחות בקרה



Consider expanding existing procedures to include using gloves, face masks, and/or gowning where such measures were not previously required.

יש לשקול הרחבה של שימוש בכפפות, מסכות ולבוש ייעודי
באזורים שזה לא נדרש בעבר

Consider further restrictions on employee access to any manufacturing area, beyond that required by CGMP regulations and recommended by Agency guidance and normal practice, to limit the possibility of contamination.

יש לשקול איסורים נוספים של כניסת עובדים לאזורי ייצור מעבר לנידרש בזמן רגיל





COVID -19 FDA Guideline- Biological products

Contains Nonbinding Recommendations

Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing

Guidance for Industry

June 2020

For biological products where manufacturing processes or materials are more susceptible to viral contamination, manufacturers should already have stringent viral control strategies in place. Potential risks from SARS-CoV-2 are likely to be mitigated by existing viral control strategies. However, FDA recommends that manufacturers perform a risk assessment of the current viral control strategy in light of SARS-CoV-2 and implement appropriate mitigation strategies.

Risk Assessment for the potential viral contamination caused by sick operator - FMEA

Risk Assessment										Risk Mitigation					
Process Step	Potential Failure Mode	Potential Effect(s) of Failure	(S)	Potential Cause(s)/ Mechanism(s) of Failure	(O)	Current Controls Measurements	(D)	RPN	Risk Accepted (Yes/No)	Recommended Action / CAPA	Expected CAPA Output	(S)	(O)	(D)	Estimated RPN after implementation of the Recommended Actions
Sampling of chemicals for the DS and of excipients for the formulation step	Contamination caused by sick operator during sampling	Presence of virus in the chemicals or excipients	3	Operator coughing or sneezing towards unprotected raw material or touching open raw materials with contaminated hands	1	1.Sampling of chemicals for the DS and of excipients for the formulation step, in the sampling room no. Grade C, (Class ISO 8) under a LFH work station (ISO 7) 2. correct gowning procedure being followed includes face mask and sterile 3. all samplers are trained and qualified.	5	15	Yes	NA	NA	NA	NA	NA	NA

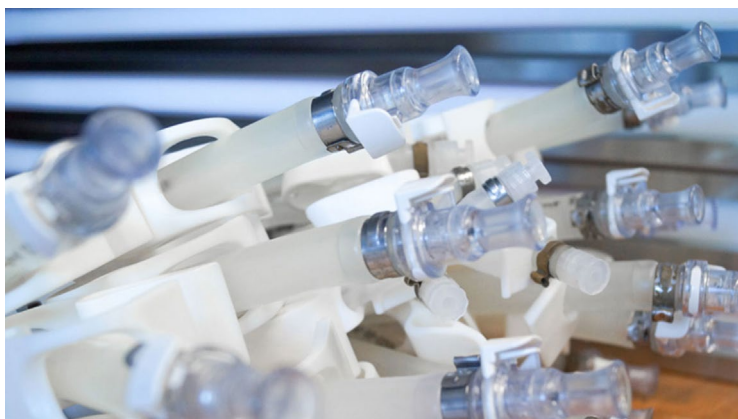
Failure Number	Process Step	Potential Failure Mode	Potential Effect(s) of Failure	(S)	Potential Cause(s)/ Mechanism(s) of Failure	(O)	Current Controls Measurements	(D)	RPN	Risk Accepted (Yes/No)
1	Sampling of chemicals for the DS and of excipients for the formulation step	Contamination caused by sick operator during sampling	Presence of virus in the chemicals or excipients	3	Operator coughing or sneezing towards unprotected raw material or touching open raw materials with contaminated hands	1	1. Sampling of chemicals for the DS and of excipients for the formulation step, in the sampling room no. Grade C, (Class ISO 8) under a LFH work station (ISO 7) 2. correct gowning procedure being followed includes face mask and sterile 3. all samplers are trained and qualified.	5	15	Yes



2	Weighing of the DS and of excipients for the formulation process	Contamination caused by sick operator during Weighing of raw material	Presence of virus in the chemicals or excipients	3	Operator coughing or sneezing towards unprotected raw material or touching open raw materials with contaminated hands	1	1. Weighing of raw material for the DS and of excipients for the formulation process, in room Class ISO 8 under a LFH work station of Class ISO 7. 2. correct gowning procedure being followed includes face mask and sterile gloves 3. During manufacturing process at least 2 validated virus clarification/ inactivation steps included 4. all operators are trained and qualified.	5	15	Yes
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7	Final filling-Connecting of product tube to filling machine and filling machine assembly	"open" manipulation during connection	Final Product contamination	5	Operator coughing or sneezing towards unprotected open DP solution unprotected open DP solution with contaminated hands	1	1. The connection performed in Class A. 2. correct gowning procedure being followed includes face mask and sterile gloves according 3. All operators are trained in aseptic work and qualified	5	25	Yes	Use of sterile welder	Limit the open manipulations
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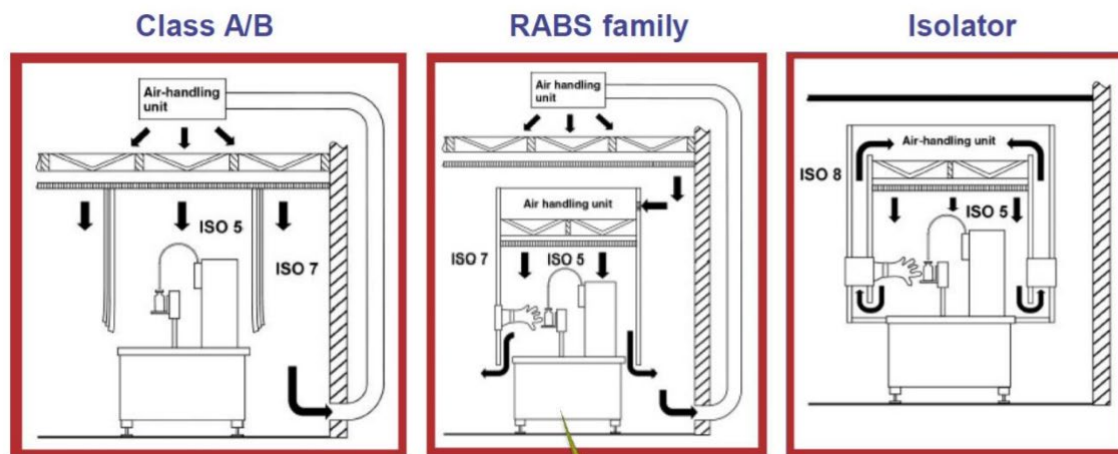


Filing of vials- Interventions	Contamination during intervention	Product contamination	5	Operator coughing or sneezing towards unprotected open DP solution unprotected open DP solution with contaminated hands during filling machine doors opening	1	1.After door opening all the empty and filed bottles in the area are rejected and the first filled bottle post intervention is tested for sterility. 2. all the filling machine exposed area including the doors are disinfected before return to filling process 3. The interventions were challenged by media fill ?? 4.All the operators are trained and qualified for aseptic technique	5	25
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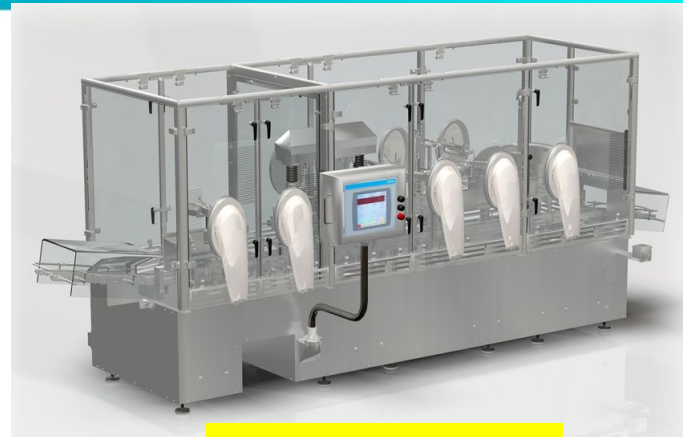
Restricted Access Barrier Systems (RABS) and isolators are beneficial in assuring the required conditions and minimizing the microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. **Any alternative approaches to the use of RABS or isolators should be justified.**

Conventional A/B filling vs. RABS vs. Isolator





Class A/B



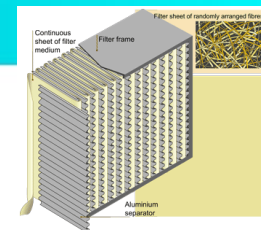
Open RABS



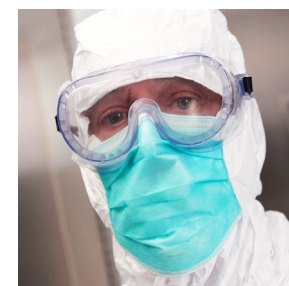
Close RABS



Isolator



HVAC system									
	HVAC failure	Product contamination	5	HVAC malfunction could cause contamination	2	1.HMI system controlled and monitored. 2. Receipt of alerts Online. 3. HVAC qualification according SOP's 4. HVAC maintenance according	1	10	Yes



Production – Filling ISO 5/6	Contamination of goggles by sick operator	Product or other operators' contamination	5	Using of contaminated goggles	1	Goggles are sanitized and disinfected between filling processes	3	15	Yes
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Production – Filling ISO 5/6	Contamination By sick operator during simultaneous gowning of two operators in ISO 5/6 gowning room	Product or other operators' contamination	5	Operator coughing or sneezing towards other operator during gowning	1	At the start of gowning procedure while entering the gowning room the operator must wear double gloves and double face masks. No physical contact between operators is allowed. part of the gowning process. While one operator is in the process of gowning on one side of the separating bench, the next operator must wait on the other side of the bench until gowning by the first operator is complete.	5	25	Yes
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14	Production – Filling ISO 5/6	Contamination From mouth and nose covered by face mask in	Product or other operators' contamination	5	Operator coughing or sneezing towards unprotected open product or towards other operator due to inefficient face mask	1	CR classic face mask gamma sterilized cat 62494 (Kimberly-clark). According to the manufacturer particle filtration efficacy of 0.1µm is 92.9%. Bacterial filtration efficacy of 3µm is 94.2%. Face masks provide barrier protection against droplets, including large respiratory particles. Most facemasks do not effectively filter small particles from the air and do not prevent leakage around the edge of the mask when the user inhales. According to the current WHO (29/03/20), Respiratory infections can be transmitted through droplets of different sizes: when the droplet particles are >5-10 µm in diameter they are referred to as respiratory droplets. According to current evidence, COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes	5	25	Yes	Consider changing the face masks to N95	Upgrade of mouth and nose protection
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Mask vs Respirator

- The available evidence was consistent to show that the use of N95 respirators and surgical masks is associated with a reduced risk of coronaviruses respiratory illness compared with no mask use, with high certainty on this beneficial effect. In moderate- to high-risk environments, especially in aerosol-generating procedures, evidence suggests that N95 respirators are associated with a more significant reduction in risk of COVID-19 infection compared with surgical masks, an effect seen in observational COVID-19 studies and experimental viral respiratory illness studies. Low-quality evidence estimates from these studies suggest a relative reduction of 50% in the risk of contagion associated with N95 respirators compared with surgical masks.

The Coronavirus is single-stranded RNA viruses (+ssRNA) enveloped virus, has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat. Furthermore, these viruses can be effectively inactivated by lipid solvents including ether, ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for chlorhexidine.

Disinfectant	Efficacy against virus
Surfanios	According Manufacturer brochure: Virus activity Adaptation of standard EN 14476 for HIV-1, PRV (model virus of HBV), BVDV (HCV model virus), Herpes virus, Rotavirus, Norovirus, Coronavirus (SARS) 15 min contact time, Influenza virus A HxNy, Vaccinia virus... - Reduction viral $\geq 10^4$ (4 log). EN 14675 : Enterovirus bovine type 1, Reduction viral $\geq 10^4$ (4 log).
Ethanol 70%	the spectrum of virucidal activity of ethanol at high concentrations covers the majority of clinically relevant viruses. <u>enveloped viruses</u> are extremely vulnerable to 70% ethanol some <u>non-enveloped viruses</u> are moderately resistant to 70% ethanol such as Rhinovirus-14, while others are highly resistant such as Enterovirus-71. Ref. Journal of Hospital Infection, Efficacy of ethanol against viruses in hand disinfection, G. Kampf
Isopropanol 70%	Same as Ethanol Isopropyl alcohol is not active against the nonlipid enteroviruses but is fully active against the lipid viruses, Ref. CDC
NaOH 0.5N	Both enveloped and non enveloped virus (HIV: human immunodeficiency virus type 1; BVDV: bovine viral diarrhea virus; CPV: canine parvovirus; BHV: bovine herpes virus type 1; POL: human poliovirus type 2; SV-40: simian virus-40; MLV: murine leukemia virus; ADV: human adenovirus type) Ref. Data from Q-One Biotech Ltd., Scotland.

- Related to Bacteria, yeast and fungi
- Nothing for Viral Contamination

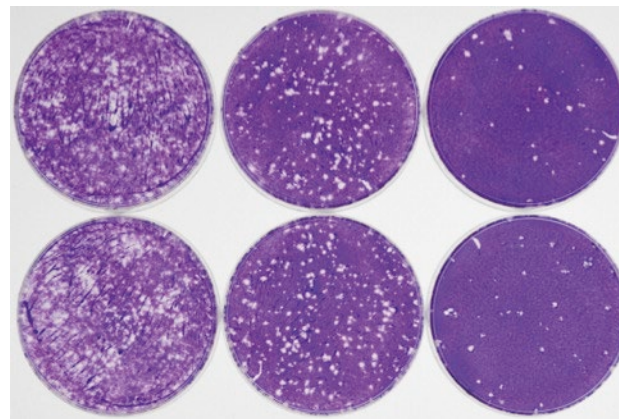


Table 4. Growth Media and Incubation Periods for Sterility Testing^a

Growth Medium	Incubation Temperature Requirements	Incubation Period	Tests for
Fluid Thioglycollate Medium (FTM)	32.5 ± 2.5° C Requires an incubator	14 days	Anaerobic bacteria, but will also grow aerobic bacteria
Soybean-Casein Digest Medium (SCDM)	22.5 ± 2.5° C	14 days	Aerobic bacteria and fungi

Adapted from USP <71>

^aMedia must be validated with the following microbial species (strains specified in USP <71>): *S. aureus*, *Bacillus subtilis*, *P. aeruginosa*, *C. sporogenes*, *C. albicans*, and *Aspergillus niger*.





Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing

Guidance for Industry

June 2020

Drug manufacturers should determine if SARS-CoV-2 could adversely affect the safety or quality of their materials, components, drug product containers and closures, in-process materials, and drugs if they were to become contaminated with the virus. The risk assessment should consider the known characteristics and studies of this family of viruses as well as the drug types and their characteristics (e.g., drug product or API, sterile, non-sterile, solids, powders, liquids, large or small molecule). Lots or batches of components, drug product containers and closures, in-process materials, and/or drug products determined to be adversely affected in terms of safety and quality must not be released for further manufacturing or for distribution. Such items must be properly dispositioned (e.g., quarantined pending appropriate re-evaluation or reprocessing, or rejected). Lots or batches of APIs determined to be adversely affected in terms of safety or quality must not be distributed. Such lots or batches should be properly dispositioned (e.g., quarantined pending appropriate re-evaluation or reprocessing, or rejected).

FDA is not aware of any drugs that have been contaminated with SARS-CoV-2 or of information indicating transmission of COVID-19 is associated with drugs.

Since the COVID-19 outbreak, researchers have tried to characterise the novel coronavirus SARS-CoV-2 to better understand the pathogenic mechanisms of the virus and prevent further dissemination. As a consequence, there has been a bloom in scientific research papers focused on the behavior of the virus in different environmental contexts.

- In conclusion, our findings show that SARS-COV-2 can survive for 3 days in liquid medium or on dry filter paper
- A dry or less humid environment is unsuitable for viral survival.
- The survival time of SARS-CoV is impacted by viral stains, the types of solutions it stayed in, temperature, and viral titers. It could survive for 14 d at 4 °C, 2 d at 20 °C in dechlorinated tap water

BUSINESS CONTINUITY PLAN

Geological	• Earthquake • Landslide, mudslide, subsidence • Tsunami • Volcano
Meteorological	• Drought • Extreme temperatures (hot and cold) • Famine • Flood, flash flood, seiche, tidal surge • Geomagnetic storm • Lightning • Snow, ice, hail, sleet, avalanche • Wildland fire • Windstorm, tropical cyclone, hurricane, tornado, waterspout, dust storm, sandstorm
Biological	• Food-borne illnesses • Infectious/communicable/pandemic diseases
Accidental Human-Caused	• Building/structure collapse • Entrapment • Explosion/fire • Fuel/resource shortage • Hazardous material spill or release • Equipment failure • Nuclear reactor incident • Radiological incident • Transportation incident • Unavailability of essential employee(s) • Water control structure failure
Intentional Human-Caused	• Incendiary fire • Bomb threat • Demonstrations/civil disturbance/riot/insurrection • Discrimination/harassment • Disinformation • Kidnapping/hostage • Acts of war • Missing person • Cyber security incidents • Product defect or contamination • Robbery/theft/fraud • Strike or labor dispute • Suspicious package • Terrorism • Vandalism/sabotage • Workplace/school/university violence
Technological	• Hardware, software and network connectivity interruption, disruption or failure • Utility interruption, disruption or failure



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• BACK UP