

**ORIGINAL ARTICLE**

# Uncertified Facility (BSL 2 plus) : Its Journey through Life for Preparations and Setting up, Compliance with Biosafety Regulations, Implementation, and Registration of the Facility with the Ministry of Health, Singapore

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**ARTICLE INFO**

Received January 29, 2021

Revised February 14, 2021

Accepted February 17, 2021

**Key words**

Biological agents and toxins act

Guidelines

Implementation

Legislation requirements

Uncertified facility (BSL 2+)

**ABSTRACT**

An uncertified facility is a facility not certified, as defined in the Biological Agents and Toxins Act (BATA) in Singapore, but has met the requirements of the Ministry of Health to possess First and Fifth Schedule biological agents and toxins. This type of facility is also known as a Biosafety Level 2 Plus (BSL 2+) facility. Registration as an uncertified facility or a BSL 2+ facility requires a certain process and procedure to be sought with the Biosafety Branch of the ministry. This review, shares first-hand knowledge on the journey to achieving registration of the authors' facility. The procedure involved considerable preparation, setting up facility requirements, biosafety precautions, procedures and practices, and training and competence of laboratory users. The ministry conducted a thorough onsite facility audit to ensure that the facility requirements and biosafety procedures and practices were in place. It then issued an approval letter of possession for the first-time use of biological agents and registered the laboratory as an uncertified facility. The expectation is that the comprehensive information shared may be of great benefit to other facilities with similar interests.

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**INTRODUCTION**

A novel coronavirus, the 2019-nCoV was initially identified from cluster of pneumonia cases in Wuhan, China in December 2019. Following which, cases involving the virus were also reported in many countries around the globe and Singapore was one of them. Laboratories with different interests of research, diagnosis or production in various types of industries like education, pharmaceutical, healthcare, biomedical sciences and technology may need to handle samples or materials that could potentially contain the 2019-nCoV

and/or other biological agents and toxins with high risks in their daily operations. Appropriate biosafety and biosecurity programmes will reduce or eliminate the risk of potential exposure to biological hazards as well as prevent the loss, theft or misuse of biological agents/materials and sensitive information. As such, adequate precautions must be in place to ensure that such samples or materials are handled in a safe manner and that personnel coming into contact with the samples or materials are protected.

Handling biological agents and toxins with high risks and potential causative microorganisms of diseases of public health concerns are strictly controlled in Singapore. Biomedical scientists, researchers, laboratory users and professionals from related industries have to abide by active laws in force. Government authorized

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agencies such as Biosafety Branch, the Ministry of Health (MOH), the Agri-Food and Veterinary Authority (AVA) and the Singapore Police Force (SPF) administer their related laws and as required, issue guidelines, directives, precautions and requirements for safe handling of such biological agents, toxins and materials.

### 1. The Biological Agents and Toxins Act (BATA)

The Biological Agents and Toxins act (BATA) was first read on the 19 September 2005 as Bill No 26/2005 published on 20 September 2005 and came into force on 03 January 2006 [1]. Its objectives include preventing acts of bioterrorism, establishing a strong national biosafety culture and facilitating emerging bioscience industry in Singapore.

The act prohibits or otherwise regulates the possession, use, import, transshipment, transfer and transportation of biological agents, inactivated biological agents and toxins, and to provide for safe practices in the handling of such biological agents and toxins [2].

WHO classifies microorganisms into 4 different risk

groups depending on their relative hazards for laboratory activity [3]. The BATA adopts a schedule system for risk group classification different from WHO classification. Biological agents and toxins are classified into 5 different schedules depending on their risks as shown in the Table 1. A list of biological agents and toxins of public health concern is maintained, regularly updated and available on the MOH Biosafety website [4]. For instance, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which is the virus of recent pandemic COVID-19 disease, also known as the 2019 Novel Coronavirus (2019-nCoV) falls into the schedule 1 (part II) and the Human Immunodeficiency Viruses (HIV 1 and HIV 2) fall into the schedule 1 (part I).

The law also defines the facility requirements to use or to keep high risk biological agents and toxins. Containment facility or Biosafety Level 3 facility (BSL 3) is a minimum facility requirement to handle the biological agent which falls under BATA schedule 1 (WHO Risk Group 3). The schedule 2 biological agent (WHO Risk Group 4) is to be handled in a maximum

**Table 1.** Five schedules in BATA with their descriptions and facility requirements for safe conduct of work

BATA classification	Descriptions of schedule	Facility requirements
Schedule 1 (Part I)	(1) Usually causes serious human or animal disease (high individual risk, low community risk) (2) Effective treatment and preventive measures are available	Certified BSL 3 (uncertified facility can appeal)
Schedule 1 (Part II)	(1) Usually causes serious human or animal disease (high individual risk, low community risk) (2) Effective treatment and preventive measures are available (3) Potential to be weaponized	Certified BSL 3 and protected place (uncertified facility and protected place can appeal)
Schedule 2	(1) Usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly (high individual and community risk) (2) Effective treatment and preventive measures are not usually available (3) Potential to be weaponized	Certified BSL 3 and protected place with special approval granted by the director (medical services)
Schedule 3	(1) Can cause serious human or animal disease but unlikely to be a serious hazard (moderate individual risk, low community risk) (2) Effective treatment and preventive measures are available and the risk of spread of infection is limited (3) Needs the special attention for large scale production	BSL 2 facility, equipment, practices and procedures. Specified in the approval by the director (medical services)
Schedule 4	(1) Low or no individual and community risk	Conditions of the permit granted by the director (medical services)
Schedule 5	(1) Microbial toxins (2) Potential to be weaponized	Protected palace and conditions of an approval granted by the director (medical services)

containment facility or Biosafety Level 4 facility (BSL 4). Biological agents or microorganisms with moderate or low risks fall under the schedule 3 and the schedule 4 (WHO Risk Group 2) are allowed to handle in a BSL 2 facility. To work with toxins listed in the schedule 5 requires a protected place under the Protected Areas and Protected Places Act [5].

## 2. Legislation requirements, guidelines and circulars

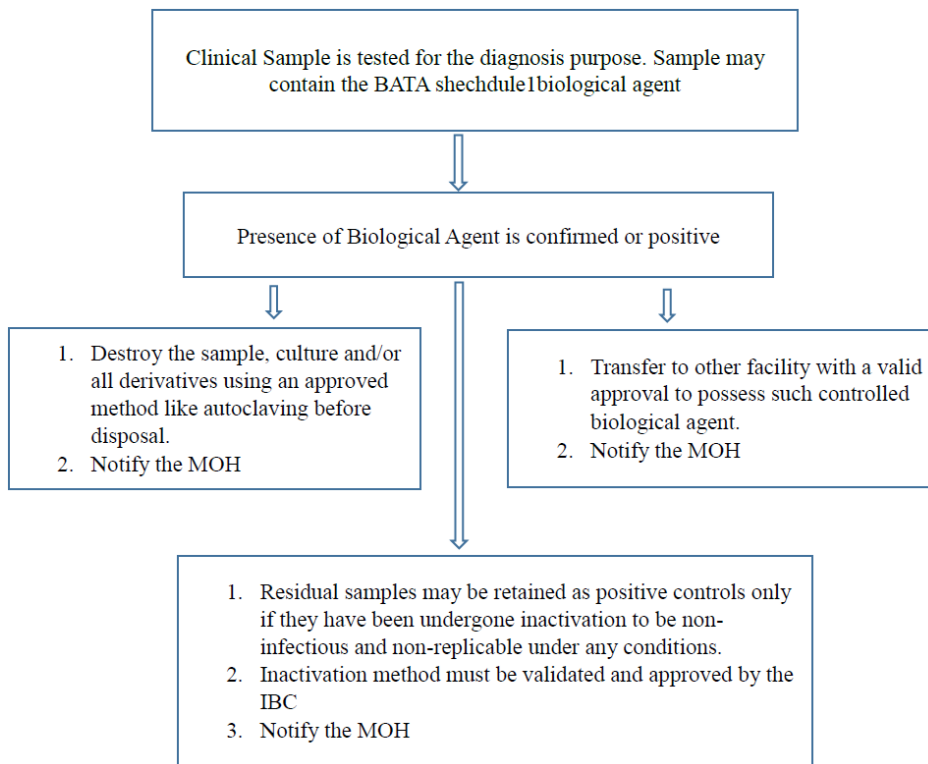
As a containment facility requirement, the BSL 3 facility is certified by a MOH-approved facility certifier (AFC) after thorough checking all structural or physical conditions under engineering aspects, administrative control measures, biosafety procedures and practices and all documents and records. The facility needs re-certification yearly or upon any design or structural change made to the facility. Having met the local requirements and international biosafety standards for a containment facility in many instances, the facility is registered with the MOH as a certified facility and ready to handle the schedule 1 biological agents inside. Keeping the BSL 3 facility operational is indeed an expensive exercise in term of budget, time and efforts. Thus, the availability of such containment facilities is limited for research activity in Singapore. However, the MOH issues the interim biosafety guidelines for research laboratories and diagnostic laboratories and personnel handling samples or materials associated with the inactivated schedule 1 biological agents.

Diagnostic laboratories are excluded from the BATA to perform their diagnostic works on human clinical samples which may contain the schedule 1 biological agents [6]. However, when the presence of the schedule 1 agents is confirmed or positive, compliance with the act BATA needs to be there. Thus, those positive samples together with any biological agents identified in samples must be destroyed or transferred to another facility with valid permit to possess and the MOH must be notified accordingly. Residual samples may be retained as positive controls only if they have been undergone inactivation. Laboratories must use a

validated inactivation method to render the residual samples non-infectious and non-replicable under any conditions. The procedure for the positive sample is briefed in the Figure 1. The inactivation method must be validated to be effective, and approved by the Biosafety Committee (with the appropriate expert committee members) or personnel with good biosafety and microbiology knowledge and experience. Information and supporting documents on the effectiveness of the inactivation method shall be kept and be made available when requested by the MOH.

Ensuring that appropriate biosafety procedures and practices are in place and that research activities are carried out in a safe manner, research facilities can make an appeal for an exemption from the BATA control for their non-diagnostic activities involving the inactivated schedule 1 biological agents. As such, adequate precautions must be in place to ensure that such samples or materials are handled in a safe manner and that personnel coming into contact with the samples or materials are protected. Having thorough reviews of the application the MOH will approve to handle the inactivated schedule 1 biological agents in a BSL 2 facility. That is the case, biosafety measures, procedures and practices are enhanced and the laboratory is registered with the MOH as an uncertified or Biosafety Level 2 Plus (BSL 2+) facility.

As information about the 2019-nCoV is rapidly evolving, the MOH has prepared an interim Biosafety Guidelines for laboratories/personnel who are transporting, processing, performing diagnostic testing and/or performing any other related activities involving samples or materials which contain or are suspected to contain the 2019-nCoV [7, 8]. Requirements for processing and laboratory testing of clinical samples are summarized in the Table 2. Viral culture and manipulation of live virus can only be carried out in a certified Biosafety Level 3 laboratory with the BSL 3 practices. Serological assay, molecular assay, for example PCR, sequencing, etc. and pathological examination are to be carried out in the BSL 2+



**Figure 1.** The procedures in brief for positive diagnostic clinical samples.

laboratory.

### 3. The company Cell ID Pte Ltd

Cell ID Pte Ltd was incorporated in March 2013 [9]. The company's moto is that "We don't do different things; we do things differently". We have strived to achieve truly near-field point-of-care (nf-POC) solutions for molecular diagnosis creating an integrated Biochip with PCR technology. This uniquely engineered Biochip does not require costly peripheral equipment to perform the tests. Instead, a laptop PC with multi-ports USB hub it can perform up to 150 tests at a single set-up anytime anywhere. The Cell ID continues to develop its proprietary platform based in-vitro POC product portfolios, which utilises microfluidics technology with integrations of biosensor and heater for POC Molecular Diagnosis - Quiz BioChip PCR for HIV-1 Viral Load Test, Malaria Parasites and COVID-19 PCR Test. All products are also equipped with auto data collection capability.

Its products, Smart Lateral-Flow technology includes

"Reader-less" HbA1c POC kit, Smart HIV, Malaria, hCG (Human Chorionic Gonadotropin) and Covid-19 IgG/IgM test kits [10]. Smart COVID-19 IgM/IgG Rapid Diagnostic Test (RDT) is a single use and rapid lateral-flow chromatography immunoassay, is a qualitative test for the detection of antibodies to SARS-CoV-2 virus in human serum, plasma or whole blood. This test is intended for use at point-of-care setting as an aid in diagnosis of infection with SARS-CoV-2. Target users are the professional in hospitals and/or clinics. A non-reactive results does not preclude the possibility of exposure to the virus. Clinical correlation is indicated with appropriate medical evaluation and possible additional testing to decide whether a diagnosis of COVID-19 is accurate.

Smart HIV 1 or 2 RDT device - Diagnostic device for Antibody to Human Immunodeficiency Virus (Colloidal Gold) is a single use rapid immunoassay, for the qualitative test for the detection of antibodies to HIV 1 and HIV 2 in human serum, plasma or whole blood. This test is intended for use, at point of care settings, as an

**Table 2.** Precautions and requirements regarding safe use of COVID-19 samples associated with SARS-CoV-2 virus extracted from the MOH Interim Guidelines (MOH Circular 17/2020)

Procedures	Precaution and requirement
Virus culture and manipulation of live virus (e.g., virus isolation, virus neutralisation assay, packaging of positive cultures)	To be carried out in a certified <b>Biosafety Level 3 (BSL 3) Laboratory with BSL 3 practices</b>
Serology assay (e.g. antigen or antibody detection) or Molecular assay (e.g. PCR or sequencing) or Pathological examination and processing of formalin-fixed or otherwise inactivated tissues	To be carried out in <b>Biosafety Level 2 Plus (BSL 2+) Laboratory</b> -Standard personal protective clothing including laboratory coat/gown and gloves; and mucosal and respiratory protection (e.g. eye protection and N95 respirator or equivalent), as indicated by risk assessment -Handling of samples is to be carried out in a certified Class II Biological Safety Cabinet (BSC) -Prevent aerosolisation of samples -Use sealed centrifuge cups or rotors that are unloaded in a Class II BSC -Secondary leak-proof containers must be used to transport or store samples within the laboratory -Personnel handling such samples must be trained or have demonstrated proficiency in microbiological practices and techniques -Emergency response procedures in place and staff are to be trained in the procedures
Sample/material inventory	Implement a robust inventory management system to ensure all samples/materials are labelled, accounted for and their movement could be efficiently tracked
Disinfectants	The following disinfectants that are effective on SARS-CoV-2 and shall be considered for use: -Sodium hypochlorite -Ice-cold acetone -Ice-cold acetone/methanol mixture (40:60) -Ethanol (70%) -Paraformaldehyde -Glutaraldehyde
Occupational health	Practise self-monitoring for fever or any other related symptoms. Personnel presenting symptoms of respiratory infections and/or has reason to believe exposure to the virus shall immediately report supervisor or the medical authorities so that they can receive appropriate medical advice or management. Any adverse incident or accident involving potential or actual exposure to the virus should be reported for evaluation and advice. MOH Biosafety must also be notified as soon as possible, within 24 hours
Biological waste management Transport	Implement procedures to meet local requirements -Triple packaging; no public conveyances for local transports; shipper must be trained -International Air shipment as category B (UN 3373) for clinical samples: as category A (UN2814) for viral cultures

aid in diagnosis of infection with HIV 1 and HIV 2 virus. Users are the professionals in hospitals and clinics. A non-reactive result does not preclude the possibility of exposure to HIV or infection with HIV. Clinical correlation is indicated with appropriate medical evaluation and possibly additional testing to decide whether a diagnosis of HIV infection is accurate. All positive specimens must be confirmed with Western Blot or other qualified ELISA test systems.

Smart hCG dip Rapid Diagnostic Test device is a One-Step urine rapid test to determine the hCG in urine specimens. There is an appearance of hCG in urine soon after conception, and its subsequent rise in concentration during early gestational growth. Intended users of this Pregnancy Test Strip are the professionals in hospitals and clinics. This device is

used to obtain a visual and qualitative result for the early detection of pregnancy.

#### 4. The research facility

The research laboratory at the Cell ID Pte Ltd is under the management of the Research and Development department led by the Founder as well as the Chief Technology Officer (CTO) of the company. Research projects involve the use and manipulation of mammalian cells, tissues or human clinical samples such as blood, sera or plasma, body fluids and secretions which may require containment work practices. Those clinical samples may be associated with the biological agents such as Human Immunodeficiency Virus (HIV), Dengue viruses, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or 2019 novel Coronavirus

(2019-nCoV) and Plasmodium parasites (malaria). Some of these biological agents are classified as the BATA schedules under the control of the act and therefore legislation requirements and compliance have become the laboratory's concerns.

## MATERIALS AND METHODS

### 1. Appointment of biosafety committee and biosafety coordinator

Every facility operator appoints a biosafety committee and a biosafety coordinator for the facility as a requirement of the BATA [2]. The institutional biosafety committee (IBC) comprises the representative of the senior management who is capable of giving decisions, the qualified biosafety coordinator, the person having expertise in microbiology and knowledge in the physical and biological sciences and laboratory practices, the person in charge of maintaining the safe and proper functioning of the facility and its equipment, and other person sufficiently qualified or experienced to help the committee carry out its function.

The IBC is responsible for the formulating biosafety policies, programmes and codes of practices as necessary, the training of staff involved in the carrying out of the proposed activity and the conducting risk assessments in related to the activity. And review of all measures, policies, programmes and codes of practice is to carry out every two years. The committee immediately informs the facility operator of any change to such biosafety measures as the committee thinks necessary.

The biosafety coordinator has attended a structured training course given by the MOH-Approved Training Provider (MOH-ATP), passed the examination to be a qualified professional and have relevant experience. The biosafety coordinator is responsible for implementing the biosafety measures, policies, and codes of practices as formulated by the IBC and conducts the in-house biosafety training programme for the authorized laboratory users.

### 2. The laboratory biosafety manual

The Laboratory Biosafety Manual has been developed and approved by the IBC as a part of the Cell ID's Biosafety and Biosecurity Programme. The manual is to comply with relevant acts and regulations and to prevent the laboratory personnel, the environment and the community from exposure to the infectious agents and materials. It provides biosafety and biosecurity information, guidelines, policies, procedures and practices for the use and manipulation of biological agents, as well as the containment and control of biohazards, potentially infectious material and genetic materials.

Operational and safety procedures described in this manual shall apply to all potential users of the facility operated by the Cell ID Pte. Ltd. No personnel is allowed to work in the research laboratory without having read this manual and attended the required training sessions provided by the company.

### 3. Facilities for containment works

The research facility itself comprises of an ISO certified clean-room, ante-room, wet laboratory and PCR laboratory. The clean-room is equipped with air blow chamber for entry and with a certified class 2 biological safety cabinet. The facility has an ample space for various types of laboratory equipment and refrigerators and freezers for the storage of biological materials. The facility has implemented safety facilities such as safety shower, hand wash basin, eye-wash station, chemical and biological spills kits, first-aid boxes, storage cabinets for chemical and flammable, etc. A CCTV camera is installed pointed to the laboratory main door. Hazard warning signs - biohazards, chemical hazards, fire hazard, etc. under globally harmonized system (GHS) are posted on where appropriate laboratory doors, instruments, equipment, cupboard, refrigerators, freezers, bottles and containers.

The clean room is usually designed to be positively pressurized. Outward airflow or positive room pressure

is an issue for biosafety. The MOH auditors have pointed out the issue during their inspection. This is a conceptual conflict between clean-room technology and biosafety concern. The ducted biological safety cabinet is used as a part of room exhaust as well. The clean-room has been adjusted to get negatively pressurized whenever it is in operation. Negative pressure serves to contain any aerosols within the room thus minimizing contamination of the external environment and reducing risks. A pressure monitoring device is installed near the entrance of the clean-room and the room pressure is closely monitored and documented. Additionally, a strict practice is applied that all works and procedures involving biological agents and materials must be done inside the biological safety cabinet.

The biological safety cabinet (BSC) is kept functioning and well maintained. It is a requirement to get the BSC inspected, serviced and certified by a qualified professional every year. And it is also requirement for autoclaves and pressured vessels to be inspected and tested by an approved contactor. Authorized users are responsible as a part of their work for maintenance of various laboratory equipment.

#### 4. Laboratory access control

Access to the laboratory is strictly controlled and approved by the CTO. Authorized users are trained in biosafety and biosecurity to be competent for safe working inside the laboratory. Visitors are informed of possible risks inside the laboratory and are accompanied with the authorized user all times. A log book of laboratory access is maintained and updated.

Appropriate personal protective equipment (PPE) must be applied to enter the laboratory. Laboratory coat or disposable gown, gloves, N95 mask, goggles, hair net and closed toe shoes or shoes covers are available in the ante-room. All laboratory users wear the personal protective equipment before entering the laboratory. The PPE are not allowed at non-laboratory areas. Before leaving the laboratory, the PPE are

discarded into the biohazard waste bin and users wash their hands properly.

#### 5. Risk assessments

A risk management system must be in place to prevent accident or loss of lives and to improve overall workplace safety and productivity. The IBC is responsible to conduct risk assessments in relation to the activity proposed to carry out and advises the facility operator the safety control measures required. We comply with the Workplace Safety and Health (Risk Management) Regulations [11] and conduct the activity-based risk assessment procedures and the 5×5 risk matrix method [12]. By nature of work, the biomedical laboratory is full of risks. Risk could be biological, chemical, radioactive, mechanical, physical, fire and electrical. All possible risks need to be identified, evaluated and controlled. Safety in laboratory is a combination of appropriate risk management system, engineering controls and technical facilities, administrative controls and safety procedures and practices.

For conducting the microbiological risk assessment, simple reference to the risk grouping for a particular biological agent is insufficient; other factors are also considered. We follow the procedures in the WHO biosafety manual [3]. Factors include the pathogenicity of the agent and infectious dose, potential outcome of exposure and routes of infection, stability of the agent in the environment, concentration and volume of material to be manipulated, presence of a suitable host (human or animal), effective treatment regimes, availability of effective prophylaxis or therapeutic interventions and laboratory activities planned.

#### 6. Staff training and competency assessment

All potential laboratory users are required to attend an in-house training before they start working inside the laboratory. This policy statement is clearly defined in the laboratory biosafety manual. The in-house training programme has been developed and implemented in accordance with the training policy drawn

up by the Institutional Biosafety Committee (IBC). The programme is expected to equip users with sound foundations for working safely in the BSL 2+ laboratory. Continuing efforts to upgrade knowledge or skill in biosafety measures and nurturing appropriate safety practices are ultimate goals of the training programme. Legislation requirements and regulations related to biosafety play crucial roles and users need to know them. Additionally, international guidelines and circulations or instructions issued by local authorities are also applied. No two facilities are the same in design and structure, administrative processes, and adopted biosafety practices. Orientation to the facility may be unique and a user's familiarization with the facility will be of great value.

The in-house training programme covers the curriculum, not limited to biosafety principles and concepts, legislation requirements – BATA, guidelines, facilities and control measures, procedures and Practices – Good Microbiological Practices (GMP), safe handling, storage, disinfection, waste disposal, biological and activity-based risk assessments, safe use of lab equipment and maintenance – BSC, Centrifuge, etc., use of personal protective equipment (PPE) and emergency response procedures – biological spills, incident/accident reporting. Upon completion of the training, all laboratory users sit for a competency assessment test. The test is a one-hour written test and its passing score is at least 70%.

### 7. Biosafety procedures and practices

All procedures and practices are intended to eliminate or minimize the exposure of research personnel and other persons and the environment to potentially hazardous agents or materials. Good microbiological practices are fundamentally applied. Laboratory procedures are carefully performed to minimize generation of aerosols, spills and splashes. Use of sharp items is limited and totally banned for some activities involving certain biological agent such as HIV viruses.

It is very important to keep common equipment such as the BSC, the centrifuge and the autoclave functioning well. Safe use and proper maintenance of laboratory instruments and equipment are seriously controlled. Standard operating procedures (SOPs) for all instruments are readily available. Make sure service records, maintenance regimes and inspection or certification of equipment are regularly performed and documented.

### 8. Biological agent inventory

A robust inventory control system is in place. Biological agents and materials are registered on arrival. A storage system for the ease of retrieval – packing, labelling, storage positioning is organized. Biological agents are stored in freezers under lock and keys and controlled by the responsible person. Inventory records include quantity received, withdrawn and balance with relevant dates. Access to biological agents is allowed only for the authorized users; inventory records are updated upon withdrawal making the movement of the stored materials traceable all times.

### 9. Biological waste management

Biological waste containers must be covered and marked with the biohazard label. Avoid overfilling. The scientists and the laboratory users ensure good housekeeping for all biological wastes under their jurisdiction. Biological wastes and contaminated material are autoclaved or decontaminated before leaving laboratory. Autoclaving at 121°C for 15 mins is the method of choice for sterilization. Functioning of autoclaves is tested and controlled routinely by the biological indicator or spore strips method.

Biological wastes which cannot be autoclaved or spill debris are chemically decontaminated with 1:10 bleach solution for at least 20 mins. Chemically treated waste which is toxic industrial waste and is disposed of by licensed waste collector.

Biologically contaminated sharps shall be placed in appropriate sharps containers that are labeled



“biohazard”. Sharp waste container should not be overfilled. Sharp boxes are put in the separate biohazard bag, labelled and disposed of by incineration only through the licensed waste collector. Use of sharps is not allowed especially for HIV work.

## 10. Emergency responses

Biological spills are attended immediately. Laboratory users are trained how to respond to the spills conducting drills in various scenarios. Spills may happen in the open laboratory, in the BSC, in the centrifuge or in the transfer hatch. However, for major or big spills the biosafety coordinator assesses and organizes the cleaning up procedures. Freshly prepared 1:10 bleach or 0.5% hypochlorite is used for disinfectant with minimum contact time 20 mins.

Any incident or accident involving biological agent is investigated, recorded and reported using the incident notification form Figure 2. Risk assessment related to the activity is reviewed and updated. Measures to prevent future incidents are considered. In case of laboratory acquired infection (LAI) and that the scheduled biological agents were involved the MOH is reported within one week.

## 11. Occupational health and medical surveillance

To work with materials of human origin (human blood, tissues, body fluids, cell lines etc.), a Hepatitis B immunization is needed. Screening of the antibody level is checked after six months of injection. Other vaccination requirements are as advised by the medical doctor. All laboratory personnel practise self-monitoring for fever or any other related symptoms. Personnel presenting symptoms of respiratory infections and/or having reason to believe that they were exposed to the virus immediately report the matter to the supervisor so that they can seek an appropriate medical attention.

For HIV Surveillance, laboratory users are sent to the designated clinic for HIV testing before commencement of the HIV work. And as a follow up HIV exposure management, they will be sent for HIV testing once a

year. For post incident HIV exposure whereby laboratory incidents have occurred, the affected personnel must be sent to the designated clinic for immediate medical attention. Ensure that information on how the incident happened and on possible HIV exposure are provided to the attending doctor.

## 12. Internal inspection and audit

Internal audit or inspection is arranged by the biosafety committee at least once a year. The internal inspection is conducted by the team members appointed by the IBC including the biosafety coordinator. During the internal audit, inventories and stocks of biological agents are checked, verified and signed by audit members with the date of audit.

This exercise ensures that standard operating procedures, safe work procedures, biosafety manual and risk assessments are reviewed and updated every 2 years. And all documents, equipment maintenance records, access records, inventories, reports, etc. are properly recorded and updated.

# RESULTS

## 1. Appeal for exemption from the BATA

Having organized all preparations, an appeal application for possession and use of First schedule biological agents to be exempted from the BATA is submitted to the MOH Biosafety. In the application letter we need to declare company information – what our interests of application are, what activities will be performed, what kinds of samples and biological agents will be involved, so and so forth. Lots of information and preparations are provided ensuring that appropriate biosafety procedures and practices have been implemented and that research activities could be carried out in a safe manner and that personnel coming into contact with the samples or materials are protected.

The MOH made preliminary document review on the Laboratory Biosafety Manual, risk assessments, procedures

Please complete Parts 1 & 2 then submit to the HOD / CTO. Keep a copy for personal and laboratory records. Do not leave any field blank, write N/A if not applicable.

**Part 1. Details of Involved/ Injured Person**

Full name (underline surname):

Occupation:

Contact Phone: \_\_\_\_\_ Contact Email: \_\_\_\_\_

NRIC Number: \_\_\_\_\_ Other (Specify): \_\_\_\_\_

Medical Treatment provided:

First Aid      Doctor      Hospital None      Other (Specify): \_\_\_\_\_

Name of medical treatment provider: \_\_\_\_\_ Contact email/phone: \_\_\_\_\_

**Part 2. Details of incident**

This incident was (Circle all appropriate):

Personal Injury      Property Damage      Environmental Damage      Near Miss

Biological Agent involved: \_\_\_\_\_ Date: \_\_\_\_\_ Time: \_\_\_\_\_

Incident reported to: \_\_\_\_\_ Position: \_\_\_\_\_ Date: \_\_\_\_\_

What (task) were you doing at the time of the incident?

Describe the incident (Attach a sketch if necessary). Propose solution(s) if appropriate.

(Try to describe exactly what happened. Include any particular Biological agent, chemical, process or equipment involved.)

For personal injuries, please describe the injury sustained:

Details of any damage to Property/ Environment:

Was there a witness? Name: \_\_\_\_\_ Email/Phone: \_\_\_\_\_

Incident was notified to: \_\_\_\_\_ Security Police      Fire      Other (Specify): \_\_\_\_\_

**Part 3. Corrective Actions taken by HOD or CTO or Committee to prevent similar Occurrence:**

Please specify actions taken including dates:

(Assess the incident, Identify root cause, review the RA, preventive measures, etc.)

Reporting process:

(Authority related and necessary, MOM, MOH, etc.)

Recorded by:

Name & Signature: \_\_\_\_\_ Position: \_\_\_\_\_ Date: \_\_\_\_\_

Figure 2. Incident notification form.

and practices and biosafety and biosecurity measures. Countless numbers of tele communications and emails were made for necessary amendments to meet the MOH requirements set for the uncertified (BSL 2+) facility. We put so much efforts to get all required documents done and satisfied. Next step was that the MOH fixed a date for physical inspection of the laboratory notifying us to get all preparations, records and documents ready.

The MOH also forwarded an inspection checklist for the uncertified facilities which they will be using for the inspection.

2. MOH audit or on-site inspection

Two MOH officers inspected our research laboratory on 3 July 2020. At the audit briefing session, the facility operator and management, the IBC members and

laboratory scientists were present. For document review, they made thorough checks on documents and records, explored existing safety practices implemented at the facility and asked many questions for clarifications.

Then they conducted the physical inspection of the laboratory. They donned the PPE for entry requirements and strictly followed the procedures and practices implemented at the laboratory. They spent a lot of time in the laboratory and checked hazard warning signs, laboratory house-keeping and cleanliness, clutters and physical hazards, chemical hazards and storage, electrical hazards, proper use of laboratory equipment, maintenance regimes and records, activities and sample processing, biological storage practices, bio-waste management, workplace safety facilities and safety equipment. And assessed the competence of the laboratory users how they manage biological spills. They watched the practical demonstration on cleaning up of the spill that happened in the BSC.

After inspection, their findings were briefly discussed with our team. They pointed out some gaps between current practices and the compliances or requirements for the uncertified facilities. Few minor non-conformances or gaps, here and there, were identified. Thus, on-site inspection exercise took over three hours. Rectification jobs and time allowed for corrective actions were advised in details when they have consolidated findings in the final audit report.

### 3. Rectifications and corrective actions

We received the audit report on 9 July 2020 stating that necessary rectifications are to be done and to update the MOH within three-month time. The biosafety coordinator continued to organize biosafety training programme for laboratory users. During COVID-19 pandemic, we had to avoid gathering of many people for training sessions. For the purpose of safe distancing, we arranged seating plan of one meter apart one person from another. We split laboratory users into groups and conducted many sessions to

complete the training programme.

The N95 mask fitness testing for individual laboratory user is one of the requirements. This is a yearly exercise in Singapore. We contacted the third party testing professional to do the job. Every laboratory user was tested for individual selection of N95 mask model, size and proper use of the mask. Test certificates is to submit to the MOH.

The IBC carefully reviewed the procedures and practices according to the auditors' advices and comments. The laboratory biosafety manual was updated accordingly. Biological spill drills in various scenarios – spill in the laboratory, spill in the BSC and spill in the centrifuge were conducted so that potential laboratory users demonstrated their competence and confidence in doing it. The management, the IBC and laboratory team put so much efforts collectively and we managed to get all rectification jobs done in time.

### 4. Registration and approvals

We received the in-principal approval letter dated 27 July 2020 to possess and handle the human immunodeficiency virus (the BATA First schedule biological agent) positive samples in the uncertified research facility. The approval comes with conditions to follow, most importantly, that the virus isolation and/or culture is strictly prohibited. We were advised to register the facility and to submit the application of possession of the HIV online via the Biosafety IT system at <https://www.moh.gov.sg/biosafety> within one-month time. The approval is valid for 3 years from the date of registration and is subject to renewal.

The Cell ID research laboratory has been successfully registered since 7 August 2020 as an uncertified facility (BSL 2+). And our application to possess for First-time use of biological agent has been approved by the Director of Medical Service since 11 August 2020. This approval is tied to the validity of the facility registration. Thus, to handle and possess a First or Fifth Schedule biological agents or toxins is valid in our research laboratory.

The facility still needs to comply with BATA requirements for the import of biological agent. Get a valid import permit from the MOH having declared accurately the name of item, hazardous substance code and MOH code, source of item, quantity, address of destination, the name of service provider for safe transport, etc. It is the responsibility of the importer to ensure that things are in order. The import permit is on a consignment basis and required for every time of importation.

## 5. Documentation

All standard operating procedures, safe work procedures, risk assessments and the laboratory biosafety manual need to be reviewed and updated every 2 years.

All documents, records, the IBC meeting minutes, accident/incident reports, permits, approvals and inventory records which are related to the BATA First and Fifth schedule biological agents and toxins, such as HIV 1 / 2 or COVID-19 virus, need to be retained for at least 3 years or as per required duration.

## DISCUSSION

Biosafety and biosecurity measures, no matter how small or how big, must be taken seriously by all involved. As research laboratories are to move forward and handle more novel, innovative and perhaps more virulence substances, there is a constant need to adopt safety culture in biological and biomedical research to be vigilant and adhere to good microbiological practices (GMP). The laboratory environment needs to be defined in terms of biosafety and biosecurity capabilities. A good regulatory framework have to strike a good balance between keeping research safe and being too restrictive. The requirements should not result in unnecessary cost increases, research being hampered, and scientists being discouraged from working to prevent disease outbreaks. On the other hand, the guilty offender shall be liable on conviction to a fine of up to one million Singapore dollars or to

imprisonment for a term which may extend to life imprisonment or to both [2]. Such severe penalties for convicted offenders reflect Singapore's serious commitment to biosafety and biosecurity.

It has been a stressful journey we have walked through. However, it is our great honour and we are very proud of getting our research laboratory successfully registered as an Uncertified (BSL 2 Plus) Facility. This remarkable achievement is indeed the result of the Cell ID management's commitment in biosafety and biosecurity and collective efforts every one of us has put in tirelessly.

**Acknowledgements:** Sincere appreciations go to the MOH Biosafety Branch for their guidance, assessments and on-site inspection, members of the IBC for their interest and supports, research scientists and potential laboratory users for their understanding and tireless participation in this process.

**Conflict of interest:** None

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