Assessment Tool for Key Processes associated with the Design, Construction, Operation, Maintenance and Regulation of BSL-3 Facilities in the WHO African Region

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Acronyms

ABSL-3	Animal Biosafety Laboratory
ACDP	Advisory Committee on Dangerous Pathogens
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSCII	Biological Safety Cabinet – Class II
BSL-3	Biological Safety Level 3
CDC	Center for Disease Control
CCTV	Closed Circuit Television
EDP	Emerging Dangerous Pathogen
EDPL	Emerging Dangerous Pathogen Laboratory
EDPLN	Emerging and Dangerous Pathogen Laboratory Network
HEPA	High-Efficiency Particulate Air
HVAC	Heating, Ventilation, Air Conditioning
NIH	National Institutes of Health
SOP	Standard Operating Procedures
UPS	Uninterruptable Power Supply
URS	User Requirement Specification
WHO	World Health Organization

Executive Summary

The WHO Emerging and Dangerous Pathogen Laboratory Network (EDPLN) in Africa aims to provide a diagnostic service for a range of pathogenic agents including Ebola virus, Marburg virus, Crimean-Congo haemorrhagic fever virus, Lassa fever virus, Rift Valley fever virus, Lujo virus and Dengue virus. Due to the dangerous nature of these organisms a safe laboratory environment, such as a Biosafety Level 3 (BSL-3) BSL-3 laboratory, is required to conduct diagnostic procedures. This laboratory must be designed to ensure that the staff and surrounding area are protected from the agents handled within and must be able to be run in a sustainable fashion.

Current international regulations governing laboratory design and related information sources are listed and described in this document. The major requirements from these documents are compared and analysed in regard to their impact on operational and maintenance issues for low-resource countries. Alternative laboratory designs and lessons learned from the Ebola outbreak in West Africa are also discussed. A short guide is given on the design, construction and commissioning processes required for BSL-3 laboratories.

Lastly, a laboratory assessment tool is provided as a framework for the assessment of BSL-3 laboratories. This assessment tool is largely based on BSL-3 requirements outlined in the World Health Organization Biosafety Manual 3rd edition. Following trial assessments in Ghana, Uganda and Kenya, the tool was revised to better fit its purpose. The final version is included in this document. It is hoped that this tool will assist and guide the establishment of a safe and sustainable network of BSL-3 laboratories for the EDPLN in the African region.

This document contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization (WHO).

Introduction

Biosafety level 3 facilities are used to provide a high degree of containment for laboratories working with biological pathogens. The requirements for such facilities were originally defined in the WHO Laboratory Biosafety Manual, which was first published in 1983 and is now in its third edition. Some countries such as the United States of America (USA), Canada, Australia, South Africa and the United Kingdom (UK) have put in place regulatory frameworks to further define these facilities and have produced guidance documents specifying their design features and requirements. Since these activities have tended to be led by developed countries and they often have "gold-plated" specifications and added features provided by technical advancement to create complex, energy-inefficient facilities that require a high degree of technical expertise to construct, commission, maintain, repair and re-certify. Although these solutions work well in high-income, technologically-advanced countries with a developed biocontainment infrastructure, they may be impractical for countries which have greater financial constraints, and lack infrastructure and trained personnel. Equally important is operational and administrative control, though focus tends to be placed more on engineering control. In this regard, a facility is only as good as its staff capacities and capabilities, no matter how well equipped it is.

This document aims to meet the needs of the WHO AFRO Emerging and Dangerous Pathogen Laboratory Network (EDPLN) and provides information on the design, construction and commissioning of biocontainment laboratories for the diagnosis of a range of emerging viral pathogens such as Marburg, Ebola, Lassa fever, Rift Valley fever, Lujo, Crimean-Congo haemorrhagic fever and Dengue viruses. International guidance on biosafety and biosecurity is analysed to identify requirements that can be easily met in a resource-limited environment without unsustainable operational and maintenance needs. It draws upon a wide range of information sources in this area and experience gained in the recent Ebola outbreak to define essential BSL-3 laboratory features and an effective commissioning toolkit to ensure they are fit for purpose. The objectives of this document are to:

(a) Identify information sources for the design and construction of BSL-3 facilities;
(b) Analyse the requirements for design, construction and commissioning of BSL-3 facilities;
(c) Provide a laboratory assessment tool to assess Emerging and Dangerous Pathogen Laboratories (EDPL).

1. Information sources (guidelines, standards, etc.) used to design and construct BSL-3 facilities in the African Region

1.1 Legislation, guidelines and regulations

Extensive web research and discussions with experts yielded no information on legislation/regulations/guidance on high containment laboratory design in the African region. However, EDPLN provided legislation from South Africa, which is detailed in chapter (section 1.6). Other countries in the region are also developing legislation in this area. There is a document on clinical laboratories from Nigeria, which lists BSL-3 laboratory requirements, which was modified following US guidance. Some information was obtained about activities with genetically modified micro-organisms. The recently formed African Biological Safety Association has as one of its goals to support emerging legislation and standards in this area; http://afbsa.org/index.php/component/content/article/58-about-afbsa/strategic-plan/334-afbsa-strategic-directionhat.

Therefore, for many African countries wishing to build a BSL-3 facility, the normal course of action is to follow the WHO Biosafety Manual and guidance provided by high-income countries, who often act as donors. The main guidance documents and regulations used are from the USA, Canada, Europe and Japan. The requirements arising from many of these documents will be considered below, with comments on their practicality for resource-limited settings. These basic requirements will then be used to inform design construction, operational and maintenance issues.

1.2 WHO Laboratory Biosafety Manual

The third edition of the WHO Laboratory Biosafety Manual, (published in 2004 and now being revised), acts as the main international source of information on biosafety laboratory requirements; http://www.who.int/csr/resources/publications/biosafety/en/Biosafety7.pdf

The current WHO Laboratory Biosafety Manual contains a series of requirements for a BSL-3 laboratory, which are summarized in Table 1.

Table 1 WHO requirements for BSL-3 laboratories

Requirement	Comment
Separation	The laboratory must be separated from the areas that are open to unrestricted traffic within the building. Additional separation may be achieved by placing the laboratory at the blind end of a corridor, or constructing a partition and door or access through an anteroom (e.g. a double-door entry or basic laboratory – Biosafety Level 2), describing a specific area designed to maintain the pressure differential between the laboratory and its adjacent space. The anteroom should have facilities for separating clean and dirty clothing/PPE; a shower may also be necessary
Anteroom	Anteroom doors may be self-closing and interlocking so that only one door is open at a time. A break-through panel may be provided for emergency exit
Surfaces	Surfaces of walls, floors and ceilings should be water-resistant and easy to clean. Openings through these surfaces (e.g. for service pipes) should be sealed to facilitate decontamination of the room(s).
Saleability	The laboratory room must be sealable for decontamination. Air-ducting systems must be constructed to permit gaseous decontamination.
Windows	Windows must be closed, sealed and break-resistant.
Sink	A hand-washing station, with hands-free controls, should be provided near each exit door
Air Inflow	There must be a controlled ventilation system that maintains a directional airflow into the laboratory room. A visual monitoring device with or without alarm(s) should be installed so that staff can at all times ensure that proper directional airflow into the laboratory room is maintained.
HVAC	The building's ventilation system must be so constructed that air from the containment laboratory – Biosafety Level 3 is not recirculated to other areas within the building. Air may be high-efficiency particulate air (HEPA) filtered, reconditioned and recirculated within that laboratory. When exhaust air from the laboratory (other than from biological safety cabinets) is discharged to the outside of the building, it must be dispersed away from occupied buildings and air intakes. Depending on the agents in use, this air may be discharged through HEPA filters. A heating, ventilation and air-conditioning (HVAC) control system may be installed to prevent sustained positive pressurization of the laboratory. Consideration should be given to the installation of audible or clearly visible alarms to notify personnel of HVAC system failure. All HEPA filters must be installed in a manner that permits gaseous decontamination and testing.
Safety Cabinets	Biological safety cabinets should be situated away from walking areas and out of crosscurrents from doors and ventilation systems
Exhaust	The exhaust air from Class I or Class II biological safety cabinets (see Chapter 10), which will have been passed through HEPA filters, must be discharged in such a way as to avoid interference with the air balance of the cabinet or the building exhaust system.
Autoclave	An autoclave for the decontamination of contaminated waste material should be available in the containment laboratory. If infectious waste has to be removed from the containment laboratory for decontamination and disposal, it must be transported in sealed, unbreakable and leak-proof containers according to national or international regulations, as appropriate.
Backflow	Backflow-precaution devices must be fitted to the water supply. Vacuum lines should be protected with liquid disinfectant traps and HEPA filters, or their equivalent. Alternative vacuum pumps should also be properly protected with traps and filters.
Documentation	The containment laboratory – Biosafety Level 3 facility design and operational procedures should be documented.
Laboratory Equipment	At Biosafety Level 3, manipulation of all potentially infectious material must be conducted within a biological safety cabinet or other primary containment device. Consideration should be given to equipment such as centrifuges, which will need additional containment accessories, for example, safety buckets or containment rotors. Some centrifuges and other equipment, such as cell-sorting instruments for use with infected cells, may need additional local exhaust ventilation with HEPA filtration for efficient containment.

1.3 US Guidance: Biosafety in Microbiological and Biomedical Laboratories (BMBL)

The US BMBL http://www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf is probably the most influential guidance document used in the African context. In fact, its definitions of BSL-3 requirements have been directly incorporated in the Nigerian guidance document for clinical laboratories.
http://www.mlscn.gov.ng/files/mlscn_docs/LABORATORY%20DESIGN%20-%20MLSCN%20Approved%20Guideline.pdf.

The requirements and recommendations for facility design in the BMBL 5th edition are similar to those of the WHO Manual and include some good practices that do not entail excessive additional costs. However, there are specifications that entail excessive expense, which may not be practical in a resource-limited context. The list provided gives useful information for client and contractor for building such a facility, however some specifications may lead to the solutions adopted being costly. The following table is adapted from the latest edition of the BMBL.

Table 2 Requirements from the US BMBL 5th Edition

Requirement	Comment
Separate Area	Laboratory doors must be self-closing and have locks in accordance with institutional policies. The laboratory must be separated from areas that are open to unrestricted traffic flow within the building. Laboratory access is restricted. Access to the laboratory is through two self-closing doors. A clothing change room (anteroom) may be included in the passageway between the two self-closing doors.
Sink	Laboratories must have a sink for hand washing. The sink must be hands-free or automatically operated. It should be located near the exit door. If the laboratory is segregated into different laboratories, a sink must also be available for hand washing in each zone. Additional sinks may be required as determined by the risk assessment.
Sealed Labs	The laboratory must be designed so that it can be easily cleaned and decontaminated. Carpets and rugs are not permitted. Seams, floors, walls, and ceiling surfaces should be sealed. Spaces around doors and ventilation openings should be capable of being sealed to facilitate space decontamination.
Floors, Walls and Ceilings	Floors must be slip-resistant, impervious to liquids, and resistant to chemicals. The installation of seamless, sealed, resilient or poured floors, with integral cove bases should be considered. Walls should be constructed to produce a sealed smooth finish that can be easily cleaned and decontaminated. Ceilings should be constructed, sealed and finished as per laboratory walls.
Decontamination	Decontamination of the entire laboratory should be considered when there has been gross contamination of the space, significant changes in laboratory usage, for major renovations, or maintenance shut downs. Selection of the appropriate materials and methods used to decontaminate the laboratory must be based on the risk assessment.
Furniture and Benching	Laboratory furniture must be able to bear anticipated loads and uses. Spaces between benches, cabinets, and equipment must be accessible for cleaning. Bench tops must be impervious to water and resistant to heat, organic solvents, acids, alkalis, and other chemicals. Joints should be smooth and easily cleaned and not creating crevices. Chairs used in laboratory work must be covered with a non-porous material that can be easily cleaned and decontaminated with appropriate disinfectant.

Requirement	Comment
Windows	All windows in the laboratory must be sealed.
Safety Cabinets	BSCs must be installed so that fluctuations of the room air supply and exhaust do not interfere with proper operations. BSCs should be located away from doors, heavily travelled laboratory areas, and other possible airflow disruptions.
Filters, Traps	Vacuum lines must be protected with HEPA filters, or their equivalent. Filters must be replaced as needed. Liquid disinfectant traps may be required
Eyewash Station	An eyewash station must be readily available in the laboratory
HVAC	A ducted air ventilation system is required. This system must provide sustained directional airflow by drawing air into the laboratory from "clean" areas toward "potentially contaminated" areas. The laboratory shall be designed such that the airflow will not be reversed under failure conditions.
Verification of Airflow	Laboratory personnel must be able to verify directional airflow. A visual monitoring device, which confirms directional airflow, must be provided at the laboratory entry. Audible alarms should be considered to notify personnel of air flow disruption.
Recirculation	The laboratory exhaust air must not re-circulate to any other area of the building
Exhaust Air	The laboratory building's exhaust air should be dispersed away from occupied areas and from building air intake locations or the exhaust air must be HEPA-filtered. Ducting carrying air from containment airs should be suitably labelled and its installation stable to prevent leaks into other spaces.
Filter Housings	HEPA filter-housings should hold the filter tightly and have gas-tight isolation dampers, decontamination ports, and/or bag-in/bag-out (with appropriate decontamination procedures) capability. The HEPA filter-housing should allow for leak testing of each filter and assembly. The filters and the housing should be certified at least annually.
Waste Decontamination	A method for decontaminating all laboratory wastes should be available in the facility, preferably within the laboratory (e.g., autoclave, chemical disinfection, or other validated decontamination method).
Primary Containment	Equipment and activities that may produce infectious aerosols must be contained in primary barrier devices that exhaust air through HEPA filtration or other equivalent technology before being discharged into the laboratory. These HEPA filters should be tested and/or replaced at least annually.
Equipment Decontamination	Facility design consideration should be given to means of decontaminating large pieces of equipment before removal from the laboratory.
Verification/ Certification·	The BSL-3 facility design, operational parameters, and procedures must be verified and documented prior to operation. Facilities must be re-verified and documented at least annually. BSC should be certified at least annually by a certified biomedical engineer and documented.

1.4 European legislation

The European legislative example may be a useful example of an overarching directive written to cover laboratories in countries across a continent from those with well-established biosafety regulations and guidance to those with no pre-existing legislative framework.
The EU Directive 2000/54 (http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32000L0054), originally produced in 1998, provides a short-list of containment measures for each class of laboratory. The measures described are either specified, recommended or not required. This is the legislative background that defines these facilities and must be met by any laboratory. Relevant items relating to laboratory biosafety from the EU directive is shown in Table 3.

Table 3 ANNEX V. of EU Directive 2000/54 of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work INDICATIONS CONCERNING CONTAINMENT MEASURES AND CONTAINMENT LEVELS (Articles 15(3) and 16(1)(a) and (b))

No.	Requirement	BSL-3
1	The workplace is to be separated from any other activities in the same building	R (Recommended)
2	Input air and extract air to the workplace are to be filtered using (HEPA) or likewise	Y (Yes) on extract air
3	Access is to be restricted to nominated workers only	Y
4	The workplace is to be sealable to permit disinfection	R
5	Specified disinfection procedures	Y
6	The workplace is to be maintained at an air pressure negative to atmosphere	R
7	Efficient vector control, for example rodents and insects	Y
8	Surfaces impervious to water and easy to clean Yes, for bench Yes, for bench and floor	Y for bench and floor
9	Surfaces resistant to acids, alkalis, solvents, disinfectants	Y
10	Safe storage of a biological agent	Y
11	An observation window, or, alternative, is to be present, so that occupants can be seen	R
12	A laboratory is to contain own equipment	R
13	Infected material including any animal is to be handled in a safety cabinet or isolation or other suitable containment	Y where the infection is by the airborne route
14	Incinerator for disposal of animal carcases	Y available

This legislation prescribes the basic specifications of a containment laboratory that are required to be met to comply with the directive and they have often been directly incorporated into national government regulations. However, in order to provide more information on how to meet these indicative requirements many governments have issued their own national guidance documents. This guidance is normally far more detailed and provides more information on how these requirements can be met, often setting out ways they can be achieved. Generally, governments can choose to "gold plate", *i.e*. set a higher level than specified by the directive, or incorporate only the basic requirements. This may reflect the position of the government regulator before the directive was incorporated (originally in 1989) which may have required a higher level of containment or may reflect the standard generally used in that country. For example: the UK modifies and expands on the above list in its guidance documents. The UK regulator has chosen to "gold plate" the recommendations from the EU Directive into specifications, such as the use of negative pressure (http://www.hse.gov.uk/pubns/books/microbio-cont.htm). Table 4 shows a comparison between EU and UK documents for selected requirements.

Table 4. Comparisons of UK and EU specifications for selected facility requirements.

Requirement (EU number from Table 3)		EU*	UK*
1	The workplace is to be separated from any other activities in the same building	R	Y
4	The workplace is to be sealable to permit disinfection	R	Y
6	The workplace is to be maintained at an air pressure negative to atmosphere	R	Y
11	An observation window, or, alternative, is to be present, so that occupants can be seen	R	Y
12	A laboratory is to contain own equipment	R	Y so far as reasonably practicable
13	Infected material including any animal is to be handled in a safety cabinet or isolation or other suitable containment	Y where infection is by the airborne route	Y when any aerosol generated

*Y = Yes, R = recommended

The situation for countries with a less developed biosafety culture would be to incorporate the directive into legislation, reflecting the lowest minimum standard approach giving a basic BSL-3 laboratory. As the biosafety culture develops it may be that countries decide to "gold plate" some of the requirements and/or develop their own guidance documents.

1.5 Other national guidelines

The requirements for the design of Biosafety Level 3 (BSL-3) laboratories are specified in guidance documents produced by many countries. These documents vary in the detail provided and the prescriptiveness and are often used as tools for regulators to ensure biosafety compliance. Leading documents are provided by the following governments and are free to download.

Canada

Biosafety Standard (2015)
http://canadianbiosafetystandards.collaboration.gc.ca/cbs-ncb/assets/pdf/cbsg-nldcb-eng.pdf

The Canadians, in their latest edition of Biosafety guidance, tried to ensure that the guidance was evidence-based by obtaining consensus for requirements from discussion groups of containment experts.

France

Ministry of Employment "Health and Safety at Work: Part II Biosafety (in French)
http://www.legifrance.gouv.fr/affichCode.do?idArticle=LEGIARTI000018530512&idSectionTA=LEGISCTA000018530514&cidTexte=LEGITEXT000006072050&dateTexte=20120720

Germany

Bundesanstalt fur Arbeitsschulz und Arbeitzmedizin (BauA) [Federal Institute for Occupational Safety and Health]

"Protective measures for specific and non-specific activities involving biological agents in laboratories"
http://www.baua.de/en/Topics-from-A-to-Z/Biological-Agents/TRBA/pdf/TRBA-100.pdf

1.6 South Africa

There are a number of regulations within South Africa pertaining to biosafety, biosecurity laboratory design and operations, which include the following;

1. Non proliferation of Weapons of Mass Destruction Act, 1993 (Act 87 of 1993), Declaration of certain biological goods and technologies as controlled goods and control measures applicable to such goods (No. 19)
   http://www.saflii.org/cgi-bin/disp.pl?file=za/legis/num_act/nowomda1993515/nowomda1993515.html&query=Non proliferation of Weapons of Mass Destruction Act, 1993 %28Act 87 of 1993%29
2. Non proliferation of Weapons of Mass Destruction Act, 1993 (Act 87 of 1993), Regulations relating to the registration of persons in control of any activity with regard to controlled goods or who have controlled goods in their possession or custody or under their control
   http://www.saflii.org/cgi-bin/disp.pl?file=za/legis/num_act/nowomda1993515/nowomda1993515.html&query=Non proliferation of Weapons of Mass Destruction Act, 1993 %28Act 87 of 1993%29
3. Occupational Health and Safety Act, 1993 (Act 85 of 1993), Regulations for hazardous biological agents (No. 1390)
   http://www.saflii.org/za/legis/consol_act/ohasa1993273/
4. Genetically Modified Organisms Act, 1997, (Act 15 of 1997)
   http://www.saflii.org/cgi-bin/disp.pl?file=za/legis/consol_act/gmoa1997286/gmoa1997286.html&query=Genetically Modified Organisms Act, 1997, %28Act 15 of 1997%29
5. Health Act (Act 61 of2003): Regulations relating to the Registration of Microbiological Laboratories and the Acquisition, Importation, Handling, Maintenance and Supply of Human Pathogens, R178 of 2012
   http://www.saflii.org/cgi-bin/disp.pl?file=za/legis/hist_reg/nha61o2003rangnr178590/nha61o2003rangnr178a2m2012665.html&query=Act 61 +health +R178

1.7 Other countries in the African Region

The Nigerian document *Laboratory Design: MLSCN Approved Guidelines,* published by the Medical Laboratory Science Council of Nigeria, which is based on the US CDC requirements (BMBL), is an excellent introduction to the design of laboratories and can be used as a source document.
http://www.mlscn.gov.ng/files/mlscn_docs/LABORATORY%20DESIGN%20-%20MLSCN%20Approved%20Guideline.pdf.

1.8 Guidance provided by funding bodies and other institutions

In recent years, there has been more detailed information developed by national laboratories, research funders, universities and other institutions to provide guidance on the practicalities of containment laboratory design. These documents give more practical information and are intended to ensure that the organisation meets national and organisational requirements and often build on organisational experience to incorporate lessons learned. Some examples are listed below:

US National Institutes of Health (NIH) Facility Design (USA)
http://orf.od.nih.gov/PoliciesAndGuidelines/BiomedicalandAnimalResearchFacilitiesDesignPoliciesandGuidelines/DRMHTMLver/Chapter2/Pages/Section2-5ContainmentLaboratoriesatBSL-3Level.aspx

UK Medical Research Council (MRC)
http://www3.imperial.ac.uk/pls/portallive/docs/1/1511900.PDF

American Biological Safety Association (USA)
http://www.absa.org/trainingtools.html

University of California Design Guides (USA)
http://www.ucop.edu/risk-services/_files/labdesign_guide.pdf

While the specifications provided in these documents are aimed at the host countries, they may have implications for some laboratories in Africa. If laboratories are undertaking studies or funded by institutions such as the National Institutes of Health or Medical Research Council, they will have to conform to their guidance.

1.9 Relevant standards

Safety Cabinets

There are various international standards used for the certification and annual testing of safety cabinets. For Class I and II safety cabinets, there is EN12469 (Europe) and NSF/ANSI 49-2002[(3)] (US), CSA Z316.3-95 (Canada), JIS K 3800 (Japan) or AS 2252 (Australia). For Class III cabinets, there are the Laboratory Safety Monograph, NIH 1979(5) (http://www.docfoc.com/laboratory-safety-monograph-1979) and the British/European Standard BS EN 12469-2000.

Laboratories

The ANSI/ASSE Z9.14 Standard focuses on performance verification of engineering controls related specifically to ventilation system features of BSL-3 and Animal Biosafety Level 3 (ABSL-3) facilities. Testing and Performance-Verification Methodologies for Ventilation Systems for BSL-3 and ABSL-3 have recently been issued. The ANSI/ASSE Z9.14-2014 Standard is the only guidance document that provides a methodology to verify ventilation systems in such facilities. The standard provides one component of a more extensive graduated and risk-based approach to reaching containment goals appropriate to the risk of the agent and the laboratory activity. (http://www.absa.org/resansiasse.html)

1.10 Commissioning documents

Commissioning is an important part of both the design and assurance that the facility operates as intended. The criteria for acceptance needs to be set out from the start of the design and tested against this expectation of performance during construction and as a complete system. Evidence of achieving the intended level of performance at commissioning acts as a base line for maintenance and ongoing performance. The Canadian *Laboratory Biosafety Guidelines, 2004 (Chapter 5)* lists some of the commissioning requirements for different levels of containment http://www.phac-aspc.gc.ca/publicat/lbg-ldmbl-04/ch5-eng.php.

While some of the commissioning describes basic visual checks others assume a complex heating, ventilation, air-conditioning (HVAC) system and the use of specialised equipment and contractors.

1.11 Biosecurity documents

The prospect of bioterrorism presents the need to protect facilities which store, work with or transfer dangerous materials from those biological materials being intentionally misused or diverted for malevolent ends. The level and types of security measures needed directly relate to the risk of the material (in this case high) and the threat of menace. Biosecurity requirements will impact on the construction of any BSL-3 facility. The actual requirements may be dependent on risk assessments carried out in regard to the security situation in a country. The two source documents that should be used are the *WHO Laboratory Biosecurity Guidance* and the *OECD Best Practice Guidelines on Biosecurity for BRCs*. Both are freely available on the web at the following URLs.

http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2006_6.pdf
http://www.oecd.org/sti/biotech/38778261.pdf

A more technical document can be obtained on request from Stockholm International Peach Research Institute *Hand Book of Applied Biosecurity for the Life Sciences*.

http://www.sipri.org/publications/covers/biosecurity.jpg/view

The impact of these documents on the construction of BSL-3 facilities will be discussed in the following chapters.

2. BSL-3 Design, construction and commissioning

2.1 Concept development/Project brief

If it has been decided that a BSL-3 laboratory is required by an organization, it will then be important to determine the purpose of the laboratory before it is designed and constructed i.e. will it be exclusively a diagnostic facility or will research programmes be included? What agents will be used in the laboratory? Will virus isolation be performed or will only genetic or immunological methods be used? What equipment will be required? Once the purpose has been established, an estimate of the potential throughput of samples will need to be defined to have an idea of items such as laboratory size, staff numbers and number of biosafety cabinets. It is important to allow for a degree of flexibility to ensure the laboratory can be expanded if required. It will also be important to determine the flow of personnel, samples and waste etc. into and out of the laboratory. All these factors need to be considered before a preliminary design can be drawn up, from which the detailed design and construction plans can be added. Funds need to be identified for construction of the facility and a budget identified for annual running costs (energy, salary of non-scientific staff, maintenance, equipment and filter testing). It is estimated that in the US and Europe, annual running costs are approximately 10% of the initial construction costs. Training plans, including costs for staff and management, also need to be included. The availability of contractors who are both able and willing to construct the laboratory in a particular setting needs to be evaluated especially if highly technical elements are to be included in the design.

The location of the laboratory may influence the concept design, or the concept design may drive the geographical location of the facility. The project brief will have to be agreed upon at a high level, i.e. by the facility management, health ministry and/or donors and a provisional budget agreed upon which covers items such as on-going maintenance and staffing.

A general overview of the design, construction and commissioning process is given in the UK ACDP document “The management, design and operation of microbiological containment laboratories” freely available at
http://www.hse.gov.uk/pubns/books/microbio-cont.htm

2.2 Layout options appraisal

Once the project brief, available space for construction, anticipated occupancy levels and process flows have been agreed upon, then the preliminary laboratory floor plans can be developed. The location of the laboratory and associated areas (offices, entrances, toilets, decontamination facilities, sample reception etc.) can be assessed and then developed into floor plans. This will then allow engineering plans to be prepared for electrical supply, lighting, drainage, and ventilation. There may be significant constraints in the choice of layout if an existing laboratory is to be refurbished or closely associated with existing facilities.

2.3 Regulatory and performance criteria

It is important to specify the performance required from the laboratory, which the builders will be expected to meet. Some of these performance criteria will be derived from the documents listed and described earlier (Chapter 1). It may be that the regulatory specification may meet BMBL requirements or those of a specific donor as this may be the easiest way and many

construction companies may be familiar with these specifications. However, deriving acceptable laboratory specifications independently may sometimes prove more sustainable and economical. Performance criteria that can be established include:

(a) Provision of essential services;
- Biosafety Cabinets,
- Hand wash sinks,
- Anterooms,

(b) Magnitude of negative air cascades (if used);
(c) Air change rates;
(d) Temperature control/limits;
(e) Filtration specifications;
(f) Waste management capacities;
(g) Biosecurity standards to be followed;
- Safe storage,
- Access control,
- Physical security.

2.4 User requirement specification and technical specification

Once the basic concept, regulatory and performance criteria have been agreed upon, then a user requirement specification (URS) is prepared. The URS is a document listing all the features, components, process flows and operating parameters, which are required to realise the objectives of a construction project, as described in the project brief. More simply, it is a list of everything that must be considered in the design of a new facility in order for it to fulfil its intended purpose. This document will require input from facility management, scientists, facility engineers and safety representatives to ensure that their requirements are included. However, it is critical that the document does not become an expensive wish list but reflects the real needs for the laboratory.

The URS then needs to be transformed into a document with technical specifications. If the expertise to convert the URS into a technical specification is not available within the organisation, it may need to sought externally; otherwise, an experienced facilitator will be required since this document will be given to the designers to use as the basis for the laboratory design.

The document will include the necessary specifications to comply with regulations such as; those required to carry out the requisite procedures for the laboratory to carry out its function and meet local building codes (fire regulations etc.). This will include the specification of components for the laboratory including: information about maintenance demands, utilities services, benching, small equipment, biosafety cabinets, personal protective equipment (PPE), agent and chemical storage, resistance to chemicals in processes, cleaning, disinfectant and fumigation. This technical specification will be used throughout the process as a check that the laboratory is still compliant during the whole construction process. It is important for this document to be externally reviewed by laboratory experts, especially laboratory engineering experts, before acceptance.

2.5 Detailed design

The technical specification will be the source document that will be provided to the selected designer who will develop a detailed design in consultation with clients. The detailed design will include floor plans, drawings, component specifications, equipment identification and placement.

2.6 Validation/Qualification

Validation can be defined as the assurance that a laboratory meets the needs of the customer. Qualification can be defined as the action of proving that the laboratory premises, systems and items of equipment work correctly as defined in the URS. In recent years, the concepts of design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ) have been adopted by high containment laboratories from the pharmaceutical industry. These concepts have proven useful to ensure that complex designs are correctly executed. However, to do this, considerable resources and documentation are required. The definition of these components are as follows:

a) **Design qualification** – Ensure that the designers understand the URS and that the detailed design meets all the requirements and identify how this will be done and documented.(*e.g.* two Class II safety cabinets are shown in the laboratory design);
b) **Installation qualification** – Ensure that equipment is delivered and installed as specified (*e.g*. ensure the cabinet is the correct model and installed in the correct position);
c) **Performance qualification** – Ensure that equipment etc. performs consistently as specified (*e.g*. ensure the airflow filters etc. perform to specification). This will involve the generation of certificates of compliance;
d) **Operational Qualification** – Ensure that the equipment can do what is designed to do (*e.g.* ensure that the cabinet can be used to carry out the diagnostic procedures intended. This includes development of SOPs, training plans etc.).

A final “dry” run of the laboratory can be used to finally ensure the laboratory is ready to be used.

Validation/Qualification costs are often estimated at 10% of the construction costs for complex containment laboratories such as those used in the US and Western Europe. However, qualification requirements will depend on the size and complexity of the laboratory. The more components, such as; HVAC systems and autoclaves that are complex and have significant commissioning requirements, the more resources are required to commission the facility and the greater is the need for commissioning specialists. Other aspects of commissioning, such as ensuring the correct positioning and installation of an electrical socket will require less specialised staff and planning. Carrying out this process allows the client to ensure that the constructed laboratory meets the required specifications. Commissioning should be scheduled in the overall work plan for laboratory construction and may require a dedicated commissioning manager acting as a focus for the various commissioning activities. Commissioning management should ensure the timely receipt by the client of a fully functioning facility for the intended purpose.

2.7 Commissioning template

An example of a commissioning template used in UK BSL-3 facilities is shown below.

Heating/cooling and Ventilation

Component	Specific performance and checks required	Checked ok and by (initials/name)	Comments and actions
Heat generation plant			
Cooling plant			
Chilled water systems			
Refrigeration			
High temperature water systems			
Cold water systems			
Ventilation systems			
Exhaust systems			
Fuel installation			

Electrical and Control Systems

Component	Specific performance and	Checked ok and by	Comments and
High voltage power			
LV power			
Lighting installations			
Security systems			
Public address systems			
Emergency power systems			
UPS systems			
Generators/standby			
Fire and Smoke alarms			
Communication Systems			
Information systems ICT			
Building management systems			
Renewable power generation systems			

3. Analysis of guidance on operational and maintenance issues and their impact in low-resource settings.

The requirements detailed in the information sources listed (Chapter 1) are many and varied and are generally designed for developed countries. Some of the requirements are expensive to meet while others have limited cost impacts. In the African context, it is important to recognise requirements, which will require a continuous budget stream as these may make it difficult to ensure that the laboratory remains sustainable, in particular, requirements that require high operational and maintenance budgets. This section analyses and assesses requirements from the three most commonly used sources of information in terms of their impact on construction costs and continuing operational and maintenance costs. The solutions adopted in the field by Ebola Virus Disease diagnostic laboratories during the Ebola outbreak are also considered. Details of these laboratories are given in Appendix B. The analysis also considers the benefit of the requirement against the cost and practicality of its acceptance.

3.1 Analysis of requirements

The table in Appendix A shows a comparison of the basic facility biosafety requirements of the WHO, US BMBL, UK ACDP and EU Directives. Although there is general agreement between US BMBL and WHO documents, the EU Directive is much less prescriptive. The approach taken during the Ebola outbreak in West Africa was very different from manipulating specimens in a classical BSL3 laboratory. Appendix A highlights the major differences between classical BSL-3 laboratories and field laboratories used during EVD outbreak. Lessons learnt from EVD in West Africa have demonstrated other options for the design and requirements of laboratories handling dangerous pathogens.

Some basic laboratory requirements are generally accepted and have no major operational and maintenance issues such as:

(a) Separation of workplace;
(b) Provision of hands-free sink at laboratory exit;
(c) Provision of cleanable, resistant and impervious floors and benching.

Other requirements which are not necessarily included in all these documents and which have only minor operational and maintenance issues are the following:

(a) **Eyewash station** – specified by BMBL will require minor maintenance and upkeep;
(b) **Provision of anteroom** – could be for clothes change/sink not necessarily part of a pressure cascade;
(c) **Cleanable walls and ceilings** – required by BMBL, UK (for animal containment facilities) and WHO.

3.2 Impact of specific requirements on operational and maintenance issues in a low-resource context

While the requirements specified in the previous section will cause only minor operational and maintenance issues, other requirements may have a major impact on operational and maintenance budgets. These include the following:

Negative Pressure/ Directional Airflow

A negative pressure environment, with sustained directional airflow, can be provided by an HVAC system or a ducted safety cabinet. If a cabinet is used to create negative pressure, then local rules may need to be developed to control access to the room when the cabinet is running/in use, since opening doors may affect air flow into the cabinet.

Provision of negative pressure requires energy to power the fan removing the air. If air is being conditioned but not re-circulated, this air will be dumped, and new air will need to be conditioned, a process that is very energy-intensive. The magnitude of negative pressure will be specified in the design and commissioning documents. It is necessary to check this during commissioning and any indicators that are used will need to be calibrated. Indicators can be simple (flaps or ping pong balls). If magnehelic gauges are used to measure negative pressure, they will require regular maintenance and calibration. If a series of pressure cascades are defined then balancing the airflows can take some time.

The aim of negative pressure is to ensure that any aerosols produced in the laboratory do not escape from the laboratory through the door or walls, even when doors are opened. However, the requirement for negative pressure is reduced if primary containment within safety cabinets or isolators is used for all aerosol-generating processes with dangerous or aerosol-transmitted pathogens and pathogens that are aerosol transmitted then the requirement for negative pressure is diminished. However, the need for negative pressure should be considered with regard to infection and containment risk. Negative pressure was not used in Western-built laboratories in the West African Ebola outbreak and is only a recommendation in the EU Directive for BSL-3 laboratories.

Laboratories need only operate at negative pressure when activities carried out involve dangerous pathogens[1]. This will greatly reduce operational costs but will need to be clearly explained in protocols to ensure correct usage. Although this approach was used in the Noguchi Institute laboratories in Ghana, an air-conditioning system had to be run round-the-clock to prevent excessive heat gains from other equipment such as fridges and freezers.

Sealable for fumigation

This requirement includes the necessity for sealed windows as specified in the WHO Biosafety Manual and BMBL regulations. Fumigation is a process whereby a laboratory is disinfected after a major accident involving a pathogen. It may also be performed if there are significant changes in laboratory usage or as part of routine maintenance etc. Fumigation generates toxic gases or vapours such as formaldehyde, hydrogen peroxide or chlorine dioxide. Therefore, leakage during fumigation may lead to exposure to others outside the facility, which can in some cases be fatal. A facility can be demonstrated as sealable for fumigation in a number of ways. These include: (i) simple methods e.g. smoke pencils and other visual indications of leak paths,(ii) dangerous methods e.g. undertaking fumigation and checking for leaks with a detector or (iii) complex methods e.g. leak decay testing. The latter method is labour-intensive and requires specialist staff and equipment. It may also lead to

[1] Pathogens are generally classified according to their risk. Class 3 and higher pathogens are generally considered dangerous and pose a threat to human health. Classification of pathogenic organisms often depends on the country context. Examples of classification lists can be found in documents such as US BMBL, UK ACDP, EU.

damage to some facilities, which may need remedial building work to ensure compliance with the leak tightness requirement.

If specified, fumigation may be required to be carried out on a regular basis, which may entail considerable costs. The use of fumigation equipment such as hydrogen peroxide and chlorine dioxide require purchasing or hiring expensive equipment (approximately US$50,000). Formaldehyde fumigation requires trained staff or experienced contractors.

However, since the majority of Emerging and Dangerous Pathogens (EDP) used in these laboratories should/will be handled solely within primary containment, fumigation and related laboratory sealability may not be required. This will reduce laboratory construction and commissioning costs. Therefore, sealability criteria should only be used, if at all, as an indication of build quality.

High Efficiency Particulate Air (HEPA) filter of extracts

The need for a HEPA filtration of intake and exhaust air is unusually an EU requirement whereas other documentation (WHO Biosafety Manual, US BMBL and UK ADCP) focus on HEPA filtration of exhaust air, with only the UK regulations requiring filtration. However, both US BMBL and WHO Biosafety Manual stipulate that filtration of exhaust air will depend on the closeness of the laboratory to other premises and air intake facilities and the potential for aerosols being generated. If the laboratory is situated apart from other inhabited facilities (offices, hospital wards etc.) and/or unlikely to have aerosols generated outside primary containment, then HEPA filtration may not be required**.** HEPA filtration can be provided using ducting and HVAC systems although it is feasible that cheaper portable filtration units could be used and extracted through windows or walls. This approach has been used for the conversion of hospital wards into isolation units for SARS patients in South East Asia[2]. HEPA filtration could be provided by the use of a single-ducted Biosafety Cabinet (BSC) or isolator as discussed above. On commissioning and at annual inspections, as required by US BMBL, the HEPA filter would need to be tested to show that it meets specification. This requires a specialist contractor with expensive equipment (approximately US$15,000). However, simpler methods could be developed requiring less expensive hand-held equipment.

Heating and Ventilation Air Conditioning (HVAC)

HVAC systems are recommended by the WHO Biosafety Manual and BMBL for BSL-3 laboratories and not specified by other recommendations. This recommendation has the most significant cost implications for a laboratory facility. If a balanced HVAC system is installed, it will require specialist engineers, specialist commissioning and regular maintenance. It will impose a regular operating cost for electrical supply for the lifetime of the laboratory. In an environment with intermittent electrical supply, this will also require extensive use of generators. It can be argued that the benefits of an HVAC system (negative pressure room, HEPA filtered extract) can be provided, if the space is small by using a ducted safety cabinet in which all procedures with infectious agents are carried out, thereby avoiding the substantial cost and complexity of the HVAC system. This may also allow the laboratory to be switched off at a defined time after operation. If required for a laboratory, air

[2] Yuen, P. L., Yam, R., Yung, R., & Choy, K. L. (2012). Fast-track Ventilation Strategy to Cater for Pandemic Patient Isolation Surges. *Journal of Hospital Infection*, 81(4), 246-250.

conditioning may be provided by a re-circulating system. However, if such units are to be used, they must be well maintained and situated away from open-fronted safety cabinets (to avoid adverse impact on air flows) and any areas where the infectious agent is to be handled. The supply of conditioned air and extract will still need to be balanced and carefully controlled to prevent fabric damage and air scavenging, especially in a well-sealed laboratory.

HEPA filter housings

The US recommends that if an HVAC system is used it should have gas tight dampers/ decontamination ports/bag in bag out. Leak testing should be capable of being carried out annually. This demonstrates the additional commissioning, maintenance and certification costs that are required if a HVAC system is installed. There are alternative ways of housing filters such as in the ceiling of the laboratory.

Recirculation

If conditioned air is not being re-circulated, a considerable amount of expensively cooled and dehumidified air will be lost with a very high cost implication. This is impractical for a resource limited country. However, both BMBL and WHO Biosafety Manual allow recirculation of filtered air back to the laboratory.

Waste decontamination

Both WHO Biosafety Manual and BMBL stipulate that an autoclave must be used. The EU directive states that a specified decontamination method be used, which would normally be an autoclave. The WHO Biosafety Manual adds that the autoclave must be in the laboratory; otherwise, waste must be transported in sealed containers to autoclaves. Autoclaves also require commissioning and regular certification and maintenance, which can be expensive. The autoclave must be correctly sized to ensure it can deal with the waste flows from the laboratory but not be oversized. More sustainable autoclaves are slowly being developed such as solar driven models. Additionally, for waste management incinerators that meet WHO recommendations and liquid treatment systems may be other options to decontaminate waste, if used consistently and validated. These options are commonly available in EDPLN laboratories.

Primary containment equipment – biosafety cabinets/isolators

The WHO Biosafety Manual and US BMBL require primary containment for all processes involving infectious material and this approach has been used for all Ebola laboratories. EU guidance only requires primary containment for manipulations of organisms that are transmitted by the airborne route. However, it is generally accepted that primary containment equipment is a necessity for an EDPLN laboratory due to the high consequence of acquiring one of these agents. The use of biosafety cabinets allows the most hazardous processes to be restricted to a small controlled area thus reducing exposure. The biosafety cabinet most often utilised is the open-fronted Class II Biosafety Cabinet (BSCII). A BSCII can be used to protect the operator but also to avoid contamination of the working surface, which is important for work such as cell culture. BSCII impose a higher on-going burden than other cabinets, as they require regular testing and maintenance to ensure that they stay within performance specifications. Since their airflows are more complex, they are subject to more performance problems than Class I or III biosafety cabinets, therefore positioning of a BSCII

within a laboratory is important. BSCII may require regular (weekly) airflow checks and annual checking of filter efficiencies and certification. This generally requires a specialist contractor with expensive equipment (approximately US$15 000). However, simpler methodologies can be developed requiring less expensive hand-held equipment (approximately US$2 000).

The mobile laboratories that were established in West Africa for the Ebola outbreak all used isolators for primary containment without any safety concerns. They were selected as they were easy to transport, provided a high level of containment and required little commissioning or maintenance. Even though they were used with high concentrations of sodium hypochlorite, isolators used in laboratories in Sierra Leone are still functional more than 12 months later. However, it is recommended that isolator canopies should be replaced on a regular basis (every 5 years). If reactive chemicals/disinfectants are used, canopy replacement may be required more frequently. The impact of higher temperatures on canopies is currently unknown but may also reduce their life.

Verification/Certification

Annual verification of BSL-3 laboratories is recommended by the WHO Biosafety Manual and BMBL. The tests defined in the verification plan will affect the cost of the verification/certification. It will be important to define what is absolutely required since verification will probably involve testing airflow and electrical safety of safety cabinets and installation and penetrations of filters, checks on protective airflows and inspecting equipment and finishes to check for damage and deterioration.

3.3 Unspecified requirements

Many of the BSL-3 laboratory requirements listed above are given generally i.e. provision of negative pressure. However, the numerical values that need to be met for negative pressure are generally not specified in legislation or guidance but these will need to be specified in the laboratory design and checked during commissioning, operation and maintenance. The choice of a value can greatly increase the price of a facility and its operational costs. These factors include the following:

Negative pressure

If negative pressure is to be defined, it must be measurable (either by a pressure gauge or ventilation flap) and stable without risk of pressure reversal. However, it should not be too high as this will utilise more power and may potentially cause damage to fabric. Complicated pressure cascades can lead to problems balancing facilities and can increase commissioning costs, operational costs and annual certification costs for very little benefit.

Air change rate

Air change rates will need to be specified for a working area. Overly high air change rates will lead to far higher electricity costs for no benefit except for the more rapid removal of any aerosol produced from any accidents outside primary containment. Air change rates should be used to maintain the comfort of operators by reducing heat loads caused by people and equipment, removing odours and controlling relative humidity and condensation. This can be

achieved by using air change rates of as low as 6 changes per hour and potentially using carefully designed natural ventilation (if sealability is not being adopted).

HEPA filter class

The actual grade of HEPA filter to be used at BSL-3 is not specified in any of the regulations reviewed. This does not mean that the most expensive one with the highest pressure differential should be used since the higher the pressure differential, the higher the power requirement. Pre-filters can be specified to prolong HEPA filter life and reduce replacement costs. Filters should be selected to be effective under the climatic conditions of the country.

Sealability

If sealability of the laboratory space is required, an acceptable leakage rate needs to be selected. Care must be taken to ensure that the rate chosen is not unrealistic for the construction type as this could greatly increase commissioning costs and time.

Effluent treatment

The treatment of effluent from BSL-3 facilities is not stated in any guidance material mainly because no agent should reach the normal effluent system or the environment. Any liquid cultures would be autoclaved and not poured down the drain. Personnel do not normally shower out unless they are working in animal facilities where there is no primary containment, or for personal hygiene.
Some laboratories are designed to be dry to avoid requirements for effluent treatment. However, hand-washing facilities are required to be nearby.

Other equipment

Some equipment, such as transfer ports and dunk tanks, that are regularly used in laboratories to move samples in and out are not specified in regulations or standards.

3.4 Biosecurity requirements

Laboratories handling and storing EDP in biobanks are entrusted with the maintenance and exchange of extremely dangerous biological material, and as custodians there is a responsibility to ensure their safe storage and use. With the threat of bioterrorism and high crime rates, it is necessary to protect facilities that work with, store or transfer dangerous biological material and to prevent their use for malevolent ends.

The level of security required for a facility housing EDPs will have to be higher than for other BSL-3 laboratories due to the type of agents used. The severity of EDP has already been defined by their classification as high but, typically, assessment includes pathogenicity, infective dose, lethality and transmission, especially if agents are being stored. The facility must ensure compliance with national and international laws and regulations.
Biosecurity requirements will involve a range of risk management practices, many of which can be imposed without much impact on laboratory design and construction, such as personnel and data control. However, some requirements will have a major impact on the construction, operation and maintenance costs of the facility. A risk assessment will classify the biosecurity level and define a high security zone. The physical design of the facility

should reflect that requirement by applying layers of physical security and administrative controls such as:

(a) Video surveillance of lab entry and laboratories themselves;
(b) Key card access;
(c) Provision of security areas.

Physical security requirements

General security considerations will include boundary protection, good lighting, use of cameras and security staff and limited access points. Additional specific measures can be employed in moderate- and high-security zones.

General security area

The facility housing biological materials and especially EDPs should be robust and resistant to intrusions including forceful intrusion. Physical security measures should provide a barrier against theft and unauthorised access to facilities and materials held therein as described above. The general area should be equipped with access control such as manual keys or electronic key cards and should be available to all staff at the facility. Screening of personal identification (ID) information should also be employed. The general area or site may or may not be equipped with 24-hour intrusion detection systems.

Restricted area

The restricted area is characterised by an additional layer of security and access controls through which only authorised staff can pass. Access to a restricted area will require additional access barriers such as additional access codes, manual keys, key card or different ID signalling authorised access. The restricted area should not share a boundary with the public area. The restricted area should be equipped with 24-hour intrusion detection systems and have emergency response plans.

High security areas

The high security area shall be nested within a restricted area and should not share a boundary with the general security area. It should be constructed to prevent entry with common tools. The high security area is characterised by a further layer of security and access control though which only those authorised can pass. Each additional security barrier should be on different systems or control sources and remain in place or default to secure in the event of emergency such as fire evacuation/alarm. The high security area should be equipped with a 24-hour intrusion detection system and response arrangements. The construction of restricted and high security areas should be such that any apertures (windows, ventilation shafts, grilles) are sufficiently and robustly protected to prevent an individual entering by this means. Emergency exit doors should be releasable only from the inside. Local fire and safety codes also need to be complied with.

Observation window

The use of an observation window in the wall or door of the laboratory is a reasonable, low-tech, low-cost method of biosafety and biosecurity assurance. The use of closed circuit television (CCTV) is becoming more widespread in laboratories and can be used instead.

3.5 Emergency power and other requirements

Working in areas where public utility supplies likely to fail on a regular basis will require emergency backup systems to ensure that the laboratory will function when power or other supplies are lost. The maintenance of power to equipment, in particular BSCII is imperative as a loss of power interrupts airflow and compromises the safety of the user. Therefore, in planning for construction, the following should be included:

(a) Generators (with enough fuel storage to run them);
(b) Uninterruptible power supply;
(c) Water reservoir for emergency use.

4. Laboratory assessment tool for BSL-3 laboratories*

A draft laboratory assessment tool for human BSL-3 laboratories was provided for discussion at the meeting held in WHO Regional Office for Africa in Brazzaville from 27-31 July 2015. After discussion, this tool was revised and submitted for further discussion at the meeting and afterwards, by email. This tool was tested on a series of laboratory visits in Ghana, Uganda and Kenya. Revisions were made after each of the visits and the final assessment tool is shown in the next section. The aim of the checklist is to analyse existing EDPL infrastructure.

Laboratory Assessment Checklist

1 General information on the laboratory

a. Name and location of the laboratory

b. General impression on physical aspects of the laboratory (for example: security, perimeter, age of the building, etc.).

2. Standards, regulations and guidelines for laboratory design and construction

a. Do you have any national standards or guidelines you follow in regards to laboratory design and construction?

☐ Yes ☐ No

If **YES,** please indicate below the national standard you follow

b. Do you follow international guidelines for BSL-3 laboratory design and construction?

☐ Yes ☐ No

If **YES,** identify which international guidelines you follow

- ☐ WHO Biosafety Manual
- ☐ US BMBL
- ☐ UK ACDP
- ☐ Other (please specify below)

c. What standard do you use for safety cabinet certification?

- ☐ NSF/ANSI49
- ☐ EN12469:2000
- ☐ AS 2252
- ☐ JIS K 3800
- ☐ Don't know
- ☐ Other (please specify below)

Any additional comments:

3. Oversight mechanisms

a. Do you have a process for laboratory approval and certification?

☐ Yes ☐ No

If **YES,** please specify

- ☐ Governmental
- ☐ External Consultant
- ☐ Funder
- ☐ International Organisation (e.g. WHO/OIE)
- ☐ Other (please specify below)

b. Is there regular inspection/audit of containment laboratories?

☐ Yes ☐ No

If **YES,** please indicate the body that inspects/audits the laboratory

- ☐ Governmental
- ☐ External Consultant
- ☐ Funder
- ☐ Institutional
- ☐ International Organisation (e.g. WHO/OIE)
- ☐ Other (please specify below)

If **YES,** please indicate how often containment laboratories are inspected/ audited?

- ☐ Six-monthly
- ☐ Yearly
- ☐ Other (please specify below)

c. Do you have written risk assessments?

☐ Yes ☐ No

If **YES,** who approves risk assessments?

- ☐ Laboratory Scientist
- ☐ Principle Investigator
- ☐ Institute/University Biosafety Officer
- ☐ Laboratory management
- ☐ Regulator

Any additional comments:

4. Existing BSL-3 laboratories in the country

a. Are there any other BSL-3 laboratories/facilities in the country?

☐ Yes ☐ No

If **YES,** how many laboratories are there in the country?

List laboratories by human/animal/plant facilities, if known:

b. Are there any other laboratories/facilities under planning or construction?

☐ Yes ☐ No

If **YES,** list planned laboratories/facilities or those under construction.

c. Any additional comments:

5. Laboratory Use and Funding

a. What is the function of this laboratory?

- ☐ Diagnostic (D)
- ☐ Research (R)
- ☐ Production (P)

Indicate the role of the laboratory in regards to sample type: ☐ Human ☐ Animal

b. Are the pathogens handled human, zoonotic, or animal pathogens?

- ☐ Human
- ☐ Zoonotic
- ☐ Animal

c. When did the laboratory open? (indicate year)

d. What are the sources of funding of the laboratory?

	Rank
☐ Government	☐
☐ Private institution	☐
☐ Foreign organisation	☐
☐ Other (please specify below)	☐

If there is more than one source that funds the laboratory, rank them in order of funds provide:

e. What is the affiliation of this laboratory?

☐ Government ☐ Private

If Government, please indicate below which ministry.

f. Who was/is responsible for

- the lab construction?
- salary of staff?
- laboratory maintenance?

Please, indicate below:

g. Which laboratory techniques are carried out in the laboratory?

- ☐ PCR
- ☐ immunological tests
- ☐ cell culture
- ☐ viral isolation
- ☐ other (please specify below)

h. In relation to virus isolation, which pathogens are handled in the laboratory?
Please list below:

i. How many people handle pathogens in the facility?

j. List below the agents handled in the facility at present and in the future

k. Any additional comments:

6. Laboratory Entry		
	Questions	**Evidence/Comments**
a.	Is the BSL-3 lab separated from other labs used for normal activities? ☐ Yes ☐ No	
b.	Is there an anteroom to the BSL-3 laboratory? ☐ Yes ☐ No	
c.	Is there a biohazard sign on the door of the laboratory? ☐ Yes ☐ No	
d.	Is there a sign indicating contact details of the laboratory supervisor/manager? ☐ Yes ☐ No	
e.	Are the laboratory entry criteria specified? ☐ Yes ☐ No	
f.	Are the laboratory doors interlocked? ☐ Yes ☐ No	
g.	Is there pressure differential between inside the laboratory and its external environment? ☐ Yes ☐ No	
h.	Is there a breakout panel (emergency exit)? ☐ Yes ☐ No	
i	Is respiratory protection equipment (RPE) available? ☐ Yes ☐ No If **YES,** please indicate what type	
j.	Is PPE provided? ☐ Yes ☐ No If **YES**, please indicate what type?	
k	Is the PPE only used while in the laboratory and doffed in the laboratory? ☐ Yes ☐ No	
l.	Is the PPE decontaminated after use? ☐ Yes ☐ No	
Any additional comments:		

7. Laboratory Finishes, Sealability and Equipment		
	Question	**Evidence/Comments**
a.	Are the following surfaces water resistant, and cleanable? Yes No Walls ☐ ☐ Floors ☐ ☐ Benches ☐ ☐ Ceilings ☐ ☐	
b.	Are openings and penetrations sealed? ☐ Yes ☐ No	
c.	Is the laboratory sealable for fumigation? ☐ Yes ☐ No	
d.	Are the windows sealed, closed and reinforced? ☐ Yes ☐ No	
e.	Are centrifuges used? ☐ Yes ☐ No If **YES**, are the buckets and rotors sealed? ☐ Yes ☐ No	
f	Are all manipulations with the EDP carried out in a biological safety cabinet? (Class II or above) ☐ Yes ☐ No	
g.	Is there a sink for hand washing within the containment area i.e. lab or anteroom? ☐ Yes ☐ No If **NO**, indicate the location of sink for hand washing.	
h.	Is the facility fitted with an effluent decontamination system? ☐ Yes ☐ No	
Any additional comments:		

8. HVAC systems and BSC		
	Question	**Evidence/Comments**
a.	Is there a directional airflow into the laboratory? ☐ Yes ☐ No If **YES**, • How is this achieved (method)? • How is it monitored? Please indicate	
b.	Are there biological safety cabinets in the laboratory? ☐ Yes ☐ No If **YES**, please indicate below how many and the type of BSC in the laboratory	
c.	Where are BSC situated in the laboratory? Please describe.	
d	What happens to laboratory exhaust air? (please indicate)	
e.	Does this affect the room's air balance? ☐ Yes ☐ No	
f.	Is the exhaust air from the biosafety cabinet ☐ recirculated in the lab ☐ hard-ducted ☐ thimble (canopy hood) ☐ connected to the building exhaust?	
g.	Is exhaust air from the laboratory filtered (HEPA)? ☐ Yes ☐ No If **NO**, is air discharged safely?	
h.	How are the filters installed? ☐ Yes ☐ No	
i.	Is the HVAC system alarmed for positive pressurisation? ☐ Yes ☐ No	
Any additional comments:		

9. Waste and Disinfection	
Question	**Evidence/Comments**
a. Is there an autoclave for inactivating waste? ☐ Yes ☐ No If **YES,** please indicate what type of autoclave; ☐ floor standing ☐ bench top ☐ double ended	
b. Is the autoclave within the containment area? ☐ Yes ☐ No	
c. If the autoclave is located outside, how is waste transported to the autoclave?	
d. Is there an incinerator? ☐ Yes ☐ No	
e. Is there sewer backflow prevention? ☐ Yes ☐ No If **YES,** please indicate what type?	
Any additional comments:	

10. Documentation and Roles		
	Question	**Evidence/Comments**
a.	Are there SOPS or other detailed procedures available? ☐ Yes ☐ No	
b.	Are there written risk assessments? ☐ Yes ☐ No	
c.	Are laboratory workers medically assessed pre-employment? ☐ Yes ☐ No	
d.	Is medical assessment of laboratory workers carried out on a regular basis? ☐ Yes ☐ No	
e.	Are laboratory workers provided with a card identifying them as working with hazardous agents? ☐ Yes ☐ No	
f.	Does the lab have an appointed **Biosafety** officer? ☐ Yes ☐ No If **YES,** is this a full-time role? What training has she/he received? (please indicate)	
g.	Is there a **Biosecurity** officer? ☐ Yes ☐ No If **YES,** is it a full time role? What training has she/he received?	
Any additional comments:		

11. Maintenance and Certification

a. Is there a preventive maintenance plan?

☐ Yes ☐ No

b. Is a staff member responsible for maintenance?

☐ Yes ☐ No

If **YES**, please indicate staff member responsible e.g. facilities manager/engineer

c. How is this budgeted for?

Centrally ☐

From external income ☐

No specified budget ☐

Other, please define

d. Is there a regular periodic shut down for maintenance?

☐ Yes ☐ No

If **YES,** Please indicate time interval:

Six-monthly ☐

Yearly ☐

None ☐

Other, please specify

e. Who carries out the maintenance of the laboratory? Please indicate

In-house ☐

National contractor ☐

International contractor ☐

Other, please specify

f. Is there a plan for the laboratory to be certified?

☐ Yes ☐ No

If **YES,** indicate re-certification interval:

Annually ☐

Six-monthly ☐

Other, please specify

g. What support (funds, technical expertise) has been received for the construction/ operation of these facilities? Please indicate.

If funds have been received, please indicate source/donor.

12. Availability of expertise in the design, construction, commissioning and maintenance of facility and key equipment

Do you have the following services available for construction/maintenance of BSL-3 facilities?

☐ Yes ☐ No

If **YES**

Please indicate below if the expertise is sourced nationally or internationally?

	Source of Expertise	
	Nationally	**International**
HVAC engineers	☐	☐
Safety cabinet testers	☐	☐
Filter testers	☐	☐
Autoclave engineers	☐	☐
Laboratory designer	☐	☐
Specialist architects	☐	☐

Any additional comments:

Appendix A
Comparison of Major Requirements for BSL-3 laboratories.

Requirement	Classical BSL-3 Guidance Document				Field response laboratory (used in West Africa Ebola outbreak)	Comments
	WHO[a]	USA[b]	UK ACDP	EU[c]		
Separation of laboratory	Y	Y	Y	R	Y	
International biohazard warning symbol and sign displayed on laboratory access doors	Y	Y	Not specified	Y	Not specified	
Anteroom	Y	Y	Not specified	N	Y	**US BMBL** specifies self-closing doors with locks and that access to the laboratory is through two self-closing doors. An anteroom may be between the two doors. **WHO BSM** guidelines specify that anteroom doors must be self closing and interlocking so that double doors and a shower depending on the agent used in the laboratory.
Surfaces (bench, floor, walls and ceilings) impervious to water and easy to clean	Y	Y	Y	Y	Y	**UK ACDP** – Bench and walls easy to clean **EU** – Bench and floor easy to clean **US BMBL** suggests seamless, sealed or poured with cove bases.
Surfaces (bench, floor) are resistant to chemicals (acid, alkali, solvents) and gaseous agents.	Y	Y	Y	Y	Not specified	
Sealable for decontamination, including sealed windows and any penetrations in the surface	Y	Y	Y	R	N	**EU** recommends this for decontamination **WHO BSM** guidelines specify penetrations and air ducting systems (if used) must be constructed to permit gaseous disinfection. **US BMBL** guidelines suggest doors should also be sealable;
Sealable to prevent the entry and exit of invertebrates and rodents/Pest management system in place	Y	Y	Y	Y	Not specified	
Hand wash sink located in laboratory (hands-free or automated)	Y	Y	Y	N	Y	Preferably located near exit
Eyewash station located in laboratory	Not specified	Y	Not listed	Not listed	Not specified	Although not specifically indicated in **WHO BSM** guidelines for a BSL-3 laboratory, this is listed as a requirement for a BSL-1 laboratory and recommendations are cumulative as BSL increases. Additionally, the presence of an eye-wash station in a component of the safety checklist.
Inflow of air/laboratory under negative pressure to atmosphere	Y	Y	Y	R	Not specified	**US BMBL** guidelines specify a visual monitoring device for air pressure and that alarms on these devices are optional

Requirement	Classical BSL-3 Guidance Document Guidance Document				Field response laboratory (used in West Africa Ebola outbreak)	Comments
	WHO[a]	USA[b]	UK ACDP	EU[c]		
HVAC system	R	R	Not specified	Not listed	N	
Recirculation of air	Y$^{\theta}$	N	Not specified	N/A	N/A	$^{\theta}$ within lab
Exhaust air HEPA filtered	Y/N^	Y/N^	Y	Y	N	^ dependent on egress of exhaust air, HEPA filter is required if exhaust air is not away from air intake locations for buildings or occupied areas.
Backflow prevention of water supplies to the laboratory	Y	N	Not specified	Not listed	Not specified	
Biological Safety cabinets/primary containment equipment	Y	Y	Y$^{\#}$	Y$^{\#}$	**Y**	**WHO BSM** and **US BMBL** guidelines stipulate that all manipulation of infectious material must be performed in primary containment. **EU** guidelines recommend primary containment only when agent is transmitted by airborne route. BSC must be certified annually.
HEPA filter housings specified	Not specified	Y	Not listed	Not listed	N/A	**US BMBL** should have gas tight dampers/ decontamination ports/bag in bag out. Leak testing should be capable of being carried out annually.
Autoclave in laboratory	Y$^{\beta}$	Y$^{\beta}$	Y	Not listed	N	**WHO BSM** guidelines indicate that if an autoclave is not available in the laboratory, waste must be removed in appropriate sealed containers. **EU** guidelines indicate specific decontamination procedures, which will probably mean an autoclave. $^{\beta}$ preferable
Using PPE	Y	Y	Y	Y	Not specified	
Access restricted	Y	Y	Y	Y	Not specified	
Training of Staff	Not listed	Y	Not listed	Y	Not specified	
Biosafety manual for facility /laboratory*	Y	Y	Not listed	Not listed	Not specified	

Y=Yes, N=No, R=Recommended

a WHO Laboratory Biosafety Manual (WHO BSM)

b US BMBL

c EU: EU Directive 2000/54

* these requirements relate to a laboratory where an isolator i.e BSL3 cabinet (as illustrated below) is placed within a standard laboratory. Therefore some of the stringent room requirements found in other standards are not required. **Note:** Ebola samples and any organism that is considered a Class 3 pathogen should always be handled at the minimum in a Class III Biosafety Cabinet, or in a BSCII in a BSL-3 laboratory

Appendix B Ebola Outbreak Response Laboratories and Other Non-Standard BSL-3 Laboratories

During the Ebola outbreak of 2014/15 in West Africa, a number of laboratories were mobilised to allow diagnosis to be carried out close to the outbreak epicentres and Ebola treatment units. The earlier laboratories mobilised in March 2014 were designed for rapid field response in remote areas. For example is the European Mobile Laboratory (http://www.emlab.eu/) used a simple transportable plastic tent isolator for handling and inactivating viable samples and tents or buildings as the laboratory structure. The isolator used two canister HEPA filters primarily designed for use with respirators attached to a low volume respirator pump, which was used to create a slight negative pressure. More conventional HEPA filters were also installed to purify supply air.

The UK deployments in Sierra Leone in November 2014 were more planned. The three laboratories deployed in Sierra Leone were designed and operated by PHE staff and built by the UK military. These laboratories carried out PCR and lateral flow device-based diagnosis and, in some cases, clinical chemistry assays. The approach adopted in these laboratories dictated that any handling of samples containing a viable agent was to be performed in HEPA filtered isolators within the laboratory. These isolators were adapted from those commonly used for animal husbandry and had filtered inlet and exit air and a pass box for moving samples in and waste out. (Figure B1 and B2) Equipment was passed out of the isolators following disinfection using sodium hypochlorite sprays. Staff wore theatre scrubs, a disposable back fastening gown, double gloves and washable laboratory footwear. Gloves and facemasks were available if required, as per the risk assessment. The staff entrance to the laboratory was separated from the sample entrance. Since the laboratories were not mechanically ventilated, no negative pressure and HEPA filtration was used. The concept was to keep potentially contaminated areas to the bare minimum. Though cost was not a driver, reducing the size of the ventilated area reduced not only the cost of the laboratory itself but also on-going operational and maintenance costs. Flexible film enclosures were also used by other countries' mobile laboratories, including those from the United States and Canada. This isolator-based approach is one that could be considered for EDPLN laboratories in some countries or regions. The UK has published guidance on testing and maintenance of containment isolators with pathogenic organisms.
http://www.hse.gov.uk/biosafety/isolators.pdf

Modular Laboratories

Some companies build modular laboratories or container-based laboratories. These types of laboratories have been used in some African countries (Botswana, Zambia, Nigeria, Tanzania, Ghana, Kenya and South Africa) as BSL-3, mostly as TB or animal disease diagnostic laboratories.

Transportable Mobile Laboratories

A number of companies provide mobile BSL-3 laboratories, which can be transported on large articulated vehicles. This may limit their use to areas with adequate

infrastructure to handle such vehicles. However, the capacity of the laboratories themselves tends to be low due to limited internal space.

Web-based research using the search terms, mobile/modular biosafety/BSL-3 laboratory or biocontainment infrastructure yields the names and URLs of various vendors of these types of facilities. Mobile, military field laboratories have also been developed by many countries.

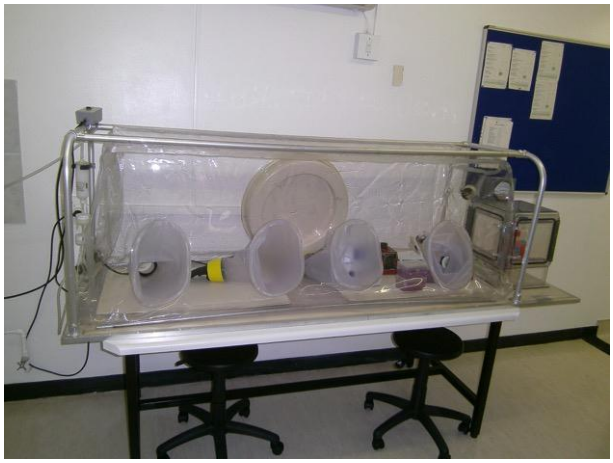

Figure 1.

Figure 2

Figure 3

Figures 1-3 from: Regional Training on Laboratory Diagnosis for Emerging and Dangerous Pathogens, 10-14 September 2012, Johannesburg, South Africa.

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