Appendix 7

EUROPEAN COMMISSION FOR THE CONTROL OF FOOT-AND-MOUTH DISEASE

MINIMUM BIORISK MANAGEMENT STANDARDS FOR LABORATORIES WORKING WITH FOOT-AND-MOUTH DISEASE VIRUS

VERSION GS40/4.2BIS

Updates to the 39th Session Standard indicated in highlight

Modifications after receipt of feedback from member States by April 17th indicated in ~~strike through~~

Proposal to the 40th Session

1. To Adopt the "Minimum Biorisk Management Standards (MBMS) For Laboratories Working With Foot-And-Mouth Disease Virus", as developed by the Biorisk Working Group of the EuFMD Special Committee on Research and presented as paper GS40/4.2bis;
2. To place the further development of the MBMS, including standards for Tier A ad B laboratories, on the programme of the Special Committee for the biennium with the expectation of revised Standard being proposed for the 41st Session

Note on the Version GS40/4.2bis

1. The Biorisk Working Group of the EuFMD Special Committee on Research reviewed the current "Minimum Standards for Laboratories working with foot-and- mouth disease virus in vitro and in vivo" which had been adopted at the 38th General Session of EUFMD on 29 April 2009 , and which superseded the prior Standards (1993 and 1985).
2. Their recommendations for changes to the Standard were then circulated in a consultation Phase, through the Secretariat, involving Biorisk managers of the FMD reference laboratories which handle live FMDV in Italy, France, Netherlands, Denmark, Germany and the UK.
3. Following their responses, the proposed Standard was sent out to the EuFMD member states in April with request to return technical comments by the 17th April.

4. Comments were received from 5 member states (UK, Ireland, Sweden, Switzerland and Denmark).
5. The technical comments were reviewed by the Leader of the Biorisk Working Group. The version GS40/4.2bis indicates the changes to the 2009 MBMS in yellow highlight , and in strike through (indicated ~~strike through~~), the changes following the response from the MS received by April 17th.
6. Specific points addressed following consultation with the MS :
   a) As "Tier 1 – 4" may cause confusion with Risk Group 1-4 and BSL 1-4, the suggestion (UK) was followed to change it to Tier A,B,C, and D.
   b) It was taken into account that in some facilities showering out is not possible and so this was changed into a recommendation (CH) ("should").
   c) As pre-heating of serological samples will not be possible in some testing regimes and requires additional validation efforts (UK). A flexible wording was chosen. ("…should … as far as possible without impairing the intended testing regime or the validity of the tests used".)
   d) Points to be considered in a future revision include:
   e) a clause on a preventive maintenance (Romania)
   f) the use of Safety Performance Indicators (UK)
   g) clarification of the role of the Biorisk Officer (CH).
   h) Comprehensive updating of the Glossary (DG SANCO)
   i) work on Sections covering Tier A and B
   j) an Annex providing examples/guidelines for inactivation procedures for samples';
   k) the use of vaporized hydrogen peroxide for FMDV inactivation, following validation .

Version 18 April 2013 Paper GS40/4.2bis

DRAFT Document

for

adoption at the 40th General Session of the European Commission for the Control of FMD (EUFMD) - April 2013

MINIMUM BIORISK MANAGEMENT STANDARDS FOR LABORATORIES WORKING WITH FOOT-AND-MOUTH DISEASE VIRUS

SECTION I.

LABORATORIES WORKING WITH FOOT-AND-MOUTH DISEASE VIRUS IN VITRO AND IN VIVO ("MBRM STANDARDS FOR FMDV LABORATORIES")

SECTION II.

MINIMUM BIORISK MANAGEMENT STANDARDS FOR LABORATORIES UNDERTAKING DIAGNOSTIC INVESTIGATIONS FOR FMD IN THE FRAMEWORK OF A NATIONAL CONTINGENCY PLAN ("MBRM STANDARDS FOR FMD CONTINGENCY LABORATORIES")

NOTE: highlighted text indicates a section that has been updated/revised compared to 2009

~~Strikethrough~~ indicates change after consultation with the EuFMD MS in April 2013

The present document does not reflect the opinion of the European Commission (DG-SANCO)

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FOREWORD

In 1985 the European Commission for the Control of Foot-and-Mouth Disease (EUFMD) at the Food and Agriculture Organization (FAO) of the United Nations adopted a document entitled "*Minimum Standards for Laboratories working with FMDV in vitro and in vivo"*. This document described a set of precautions to be taken by foot-and-mouth disease (FMD) laboratories to avoid an escape of virus. It was prepared at a time when the majority of countries on continental Europe employed systematic annual prophylactic vaccination of their cattle. Council Directive 90/423/EEC amending Directive 85/511/EEC on Community control measures for FMD made the above standards a condition for the approval and operation of laboratories handling live FMD virus (FMDV).

Although the above document dealt with all important aspects of FMD containment, it had been found necessary to review it with special reference to the need for more specific technical and general requirements as a consequence of the change in Europe to a policy of non-vaccination. The security standards as specified in the 1993 revision had to be considered as minimum requirements for FMD laboratories located in FMD-free countries with or without systematic prophylactic vaccination. Article 65 of Council Directive 2003/85/EC on Community measures for the control of FMD and repealing Directive 85/511/EEC makes the FMD-lab standards, as amended in 1993, a condition for the approval and operation of laboratories handling live FMDV.

Following the 2007 FMD outbreak in the UK that was possibly linked to the research and commercial FMD vaccine manufacture establishments co-located at the Pirbright site, EUFMD undertook to review, and where necessary to adapt, the aforementioned FMD-lab standards. The edition of the "Minimum Standards for Laboratories working with foot-and- mouth disease virus *in vitro* and *in vivo*" adopted at the 38th General Session of EUFMD on 29 April 2009 superseded the edition adopted by EUFMD in 1985 and revised in 1993.

In the years since the adoption of the 2009 version of the "Minimum Standards", it has become even more evident than before that not all the diagnostic tasks in the framework of FMD control can be carried out in laboratories meeting the "Minimum Biorisk Management Standards for Laboratories working with foot-and-mouth disease virus in vitro and in vivo". There are too few of these expensive facilities available and they are usually research laboratories with a limited sample throughput. Therefore, "FMD Contingency Laboratories" have become part of contingency plans, as foreseen in Annex XV of Council Directive 2003/85/EC. In the following, the term "FMD Contingency Laboratories" is used for laboratories which must not work with any infectious FMDV - except for virus that might be present in field samples submitted for FMD diagnosis from the country where the laboratory is situated. This means there is no risk of escape unless there is an outbreak in the field – in which case the risk posed by infected holdings by far outweighs any escape risk posed by a laboratory operating according to Section II ("FMD Contingency Laboratories") of the "Minimum Standards". In contrast to the expectations when the "Minimum Standards" were adopted in 2009, there still is no validated and fully satisfactory protocol for the inactivation of FMD samples on the suspect premises. However, inactivation of such samples in a microbiological safety cabinet in a laboratory by trained staff using lysis buffers containing chaotropic salts prior to RNA extraction poses almost no additional risk. It is therefore now included into Section II ("FMD Contingency Laboratories").

In particular in countries where the national laboratory responsible for FMD diagnosis does not meet the "MBRM Standards for FMDV laboratories" even the testing of non-inactivated samples by antigen ELISA may be justifiable, provided that the risk is controlled by appropriate measures (mainly by restricting all liquid handling steps to a microbiological safety cabinet). It allows these labs to confirm PCR results, maintain a back-up method in case PCR fails and to determine the serotype. It is up to the national competent authority to decide whether a "FMD Contingency Laboratory" is authorized to carry out antigen ELISA. This approach was applied successfully during the 2011 FMD epidemic in Bulgaria.

The alternatives would often be to forego laboratory investigations or send all suspect samples to a foreign laboratory which may be stressed to limit already by the examination of suspect samples from its own country. In particular in times of crisis, sending samples to a foreign lab creates great logistical problems. It also makes communication between laboratories and veterinarians in the field much more difficult, substantially reduces sample throughput and increases the turn-around time for decision critical diagnostic results. For effective and swift disease control, it is crucial that official veterinarians as well as the national crisis centres can contact a diagnostic laboratory easily and without a language barrier, which have staff that are familiar with national legislation and disease control systems.

Using the capacity of existing laboratories which can meet the "MBRM Standards for FMD Contingency Laboratories" can provide exactly these benefits for effective disease control, in times of crisis, and also substantially lowers the psychological threshold for submitting samples for exclusion of FMD as a differential diagnosis. In several countries, it is attempted to lower this threshold by allowing regular veterinary laboratories to carry out "exclusion diagnosis", e.g. by PCR, in cases which are not considered "suspect cases of FMD" in the legal sense but where FMD is considered a possible differential diagnosis. The measures outlined in Section II ("FMD Contingency Laboratories"), mutatis mutandis, can also help competent authorities to reduce the biorisk associated with this approach.

Following review of the former "Minimum Standards of Biorisk Management for Laboratories Undertaking Diagnostic Investigations of Low-risk samples during an Outbreak of FMD", revisions have been introduced into the new "MBRM Standards for FMD Contingency laboratories". The technical content of the "Minimum Standards for Laboratories working with FMDV in vitro and in vivo" has been left unchanged, except for minor clarifications and the now consistent use of the term "Restricted Zone" for all areas where infective FMDV is or might be handled.

What also has become clear since the adoption of the 2009 version of the "Minimum Standards" is that the task of balancing risks and benefits of laboratory work has to be seen in wider perspective, since not all EuFMD member states are free of FMD. Any standard of biorisk management should be proportionate to the prevailing disease situation in the country or zone where it is located. Therefore, a 4-tier system of minimum biorisk management standards for FMDV is currently being drafted and the MBRM standards outlined in this document refer to Tier D and C:

Tier A: General diagnostic laboratories, in FMD endemic countries

Tier B: Laboratories working with infectious FMDV, in FMD endemic countries

Tier C: Laboratories undertaking diagnostic investigations for FMD in the framework of a national contingency plan, in FMD free countries

Tier D: (Inter)national FMDV reference laboratories working with infectious FMDV, in FMD free countries

Until MBRM standards have been internationally adopted for Tiers A and B, the biorisk managers responsible for the diagnostic laboratory system in FMD endemic countries are encouraged to apply the principles of the Tier C and D MBRM as far as can be reasonably achieved. In particular, "exotic" serotypes and topotypes of FMDV should be treated with the same precautions as FMDV in a country free of the disease.

FMD free country*[1]

Activity	**Biorisk Management Standard**
Any handling of infective FMDV strains not present in the field	Tier D Standard (MBRM STANDARDS FOR FMDV LABORATORIES)
Diagnostic investigations for FMD in the framework of a national contingency plan	Tier C Standard (MBRM STANDARDS FOR FMD CONTINGENCY LABORATORIES)
General diagnostic or research work on animal samples*[2]	No FMD-related requirements *(Principles and elements of Tier C Standard should be applied according to risk assessment)*

*[1]The term "FMD free country" is used here for a country that has been recognized by the OIE as being free of FMD, with or without vaccination, even during the phase of trying to regain this status during or after an epidemic.

*[2]The term "animal samples" is used here for samples of species susceptible to FMD.

FMD endemic country

Activity	**Biorisk Management Standard**
Any handling of infective FMDV strains not present in the field	Tier D Standard (MBRM STANDARDS FOR FMDV LABORATORIES)
Infection of animals and vaccine production with infective FMDV strains present in the field	Tier B Standard *(being drafted)* *(Principles and elements of Tier D standard should be applied depending on the stage of eradication reached)*
Handling on a regular basis, including propagation in small volumes, of infectious FMDV strains present in the field	Tier B Standard *(being drafted)*
General diagnostic or research work on animal samples*[2]	Tier A Standard *(being drafted)*

SECTION I. MINIMUM BIORISK MANAGEMENT STANDARDS FOR LABORATORIES WORKING WITH FOOT-AND-MOUTH DISEASE VIRUS *IN VITRO* AND *IN VIVO*

INTRODUCTION

Foot-and-Mouth Disease (FMD) is one of the most infectious diseases known, and manipulating the virus in the laboratory without adequate precautions is a risk of environmental release. It has been shown that as few as 10 TCID can be infective to cattle by the airborne route. However, this is under experimental conditions and the low infective dose may relate to the relatively large size of aerosol droplets, which can be efficiently contained by HEPA filtration of air exhaust from facilities handling infective FMD virus (FMDV). As a consequence of the low infective dose, laboratories handling FMDV must work under high containment conditions, **in which the principle objective of the containment measures is to prevent release of virus that would give rise to animal infection outside of the laboratory (veterinary containment).**

The principles on which the containment measures are based are as follows:

– FMD virus is an animal health but not a human health hazard;

– containment measures for FMDV laboratories will differ in certain respects from those required of high containment facilities handling pathogens which present a significant human health hazard;

– effective implementation and maintenance of the containment measures will reduce the risk of an accidental release of virus to a level that can be considered acceptable in a risk management balancing those risks against the expected benefits of the services provided by such laboratory.

The containment measures were prepared on the basis of the documented evidence on the physico-chemical properties of FMDV, its inactivation kinetics, and the form and quantity of FMDV required to infect susceptible species.

Key factors in establishing and implementing a successful containment system include:

1. Physical and operational barriers to the release of FMDV that involve three containment layers and multiple fail-safe mechanisms as follows:

1.1. Primary containment layer:

– contain the live FMDV at source within closed containers or a class I, II or III safety cabinet, or

– in the case of infected animals, contain the live FMDV by physical containment in specially constructed rooms with treatment of all waste and the HEPA filtration of air;

1.2 Secondary containment layer:

– containing FMDV of infected materials and staff working with such materials within a closed and highly controlled physical environment, and

– subject solids, fluids and air to a treatment by validated procedures that will remove or inactivate FMDV;

1.3. Tertiary containment layer:

– prevent contact between the live FMDV and susceptible livestock outside containment by appropriate measures, such as restrictions placed on access of staff to such livestock.

2. Commitment by senior management:

– to provide the resources required to attain and maintain the containment measures, including the physical and human environment;

– to recognise the top priority of the management of the risks associated with facilities handling live FMDV;

– to establish and maintain a management system and a working culture in the facility that facilitates continual improvement in preventing possible release of virus, the effectiveness of containment processes and root cause analysis of possible release incidents so as to prevent their recurrence;

– to recognise and promote continual improvement.

General requirements

FMD risk management system: Each facility should establish, implement and maintain a FMD risk management system, appropriate to the level of risk associated with each of the mechanisms and routes by which FMDV could escape or be released.

Policy: The management of the facility should have in place a policy that clearly states the FMD risk management objectives and the commitment to improving the FMD risk management performance.

Risk assessment: To operate a FMD risk management system, a risk assessment system should be in place in order to:

– identify and address the risks (likelihood and extent of impact) of release or escape of FMDV by each facility (plant);

– define the circumstances which would trigger a new or revised assessment, for example plans to construct new or modify existing facilities , changes to the programme, changes to volume of activities, following incidents or as a result of elevated levels of biosecurity threats to the facility.

Hazard identification: The Hazard identification system should identify the situations, and other hazards, associated with the work of the facility that may impact on the risk of FMDV release, including emergencies (such as electrical failure, fire, flood, medical emergencies etc). The requirements in this standard do not necessarily identify all hazards that may occur, but are written to reduce the risk associated with the hazards in facilities handling live FMDV.

The main sources of FMDV are:

– diagnostic specimens,

– infected tissue cultures,

– infected laboratory animals, e.g. baby mice and guinea pigs,

– laboratory based physical and chemical processing of large quantities of virus, and

– infected pigs, cattle, sheep, goats and other susceptible large animals.

The principal routes by which the FMDV may escape or be carried out from laboratories include:

– personnel,

– air,

– liquid effluent,

– solid waste,

– equipment, and

– samples and reagents.

Although RNA derived from FMDV may still be infectious under very specific conditions, for practical purposes samples can be considered "inactivated" after an approved treatment with an appropriate lysis buffer and a disinfection of the sample tube by an approved method. However, as a precaution, such samples should not be handled without appropriate risk management measures, which must, in particular ensure that such samples are at no stage of processing added to cell cultures or injected into animals, except in laboratories meeting the ""Minimum Biorisk Management Standards for Laboratories working with foot-and-mouth disease virus *in vitro* and *in vivo"*

Risk control: Under the direct responsibility of the management of each facility (plant), the hazards which could lead to a risk of FMD escape should be identified, quantified, prioritised and control options identified. The requirements indicated in this Standard should be considered a minimum, and do not release the management of each facility from the responsibility to undertake a formal risk assessment process.

Special attention should be given to:

– replacement and reduction in use of live virus where possible;

– security and recording of access to the facility;

– security check of personnel handling live FMD virus;

– the responsible behaviour of personnel within and when they leave the laboratory, including the use of changing and showering facilities;

– the application of rules for primary containment;

– the maintenance of the physical containment including the air handling systems to ensure a negative air pressure where virus is manipulated and the effective particulate filtration of exhaust air;

– the decontamination of effluent;

– the disposal of carcasses in a safe manner;

– the decontamination of equipment and materials before removal from the Restricted Zone.

Use of alternative procedures: The use of alternative procedures for inactivation of FMD virus to those specified in this Standard is permissible provided that the information from the validation of the process has been examined and found equal or superior in performance to those currently specified. Decisions on equivalence of the proposed procedures can be made by national competent authorities. However, national authorities have to inform the EUFMD

Standing Technical Committee of such decisions and their scientific basis, which will be reviewed and findings published in the "*Report of the Sessions of the EUFMD Standing Technical Committee.*"

Residual Risk: The residual risk is the risk of a consequential release of FMDV, after application of the control measures. The Biorisk Officer (BRO), management and ultimately the national regulatory body should consider the overall biorisk management system together with the hazard identification and risk control procedures, and identify if there are residual risks requiring either more effective controls to be put into place, or work to be suspended.

Authorization of laboratories in respect to FMD:

In respect to work with FMDV, laboratories may be authorized by the competent authorities to carry out one or more of the following types of work:

(1) infection of experimental and/or large animals with FMDV;

(2) Manufacturing activities that involve the production of large amounts of infectious FMDV, e.g. large scale virus production for the production of antigen banks or FMD vaccines at a capacity greater than 10 litres of cell culture in monolayers or suspension that may reach many thousands of litres;

(3) activities involving the propagation of infectious FMDV, but are limited to 10 litres of cell culture, and during which the FMDV is enclosed in containers which can be effectively autoclaved or disinfected;

(4) to test diagnostic samples for FMDV antigen by ELISA and related methods

(5) to test diagnostic samples for FMDV genome by PCR and related methods

(6) to test diagnostic samples for antibody to FMDV by ELISA and related methods

(7) to apply on the genome of FMDV methods of molecular biology that do not involve live FMDV manipulation

Laboratories carrying out the type of work mentioned under points 1, 2 and 3 must comply with the "MBRM Standards for FMDV Laboratories".

In accordance with EU legislation, and in most cases national legislation, the manipulation of live FMDV requires a mandatory authorisation by the competent authority.

The FMDV-associated risk of laboratories carrying out the type of work mentioned under points 5, 6 and 7 is usually much lower, while the risk associated with the activity mentioned under point 4 is intermediate. However, in case the laboratory tests field samples of national origin, there is no FMDV related risk as long as the disease is not present in the country. In case of an outbreak, the main risk is posed by the infected holding and the risk of a laboratory escape must be controlled by appropriate measures (see Section II).

SPECIFIC REQUIREMENTS

The requirements below are intended to assist self-assessment, biorisk audit and inspection of facilities.

I. Management

Specific management requirements:

1. *Biorisk policy, delegation of responsibilities and communication*: The management of a facility is ultimately responsible for biorisks (biosafety and biosecurity) of its premises. The management should therefore define and document roles, responsibilities and authorities related to biosafety and biosecurity management in a formal policy statement and communicate this to all staff members.
2. *Formal process of Risk assessment / threat assessment*: The management should ensure that a formal process is in place to conduct, review and update a risk assessment. The need for a structured security threat assessment should be considered for each facility.
3. *System for continual improvement:* The management should put a system in place to guarantee that biosafety and biosecurity procedures and elements are thoroughly reviewed and audited on a regular basis. Records should be maintained of findings of audits, including actions taken to comply with the containment policy.
4. *Standard operating procedure (SOP)*: A system should be in place to maintain a complete set of SOPs for all operational processes that are considered critical to the containment of FMDV.
5. *Biorisk Officer(BRO)*: It is the duty of the management to properly monitor the biosafety and biosecurity by appointing a BRO (Biosafety / Biosecurity Officer), arranging for a deputy or replacement, and creating the necessary framework conditions in the facility. To ensure that biosafety and biosecurity is given full consideration in its activities the management should carefully define the status, duties and responsibilities of a BRO:
   (a) The BRO should report directly to the top management representative (Director-General, site Director or similar) and should have authority to stop the work in the facilities in the event that it is considered necessary to do so.
   (b) The status of the BRO should ensure his/her independence and the absence of any potential conflict of interest.
   (c) Adequate financial and personnel resources should be allocated to the BRO to carry out his or her duties.
   (d) The BRO should have the possibility of a direct link to the competent authorities responsible for the enforcement of biosafety / biosecurity regulations within the country or geographical/administrative area.
   (e) The BRO should have appropriate training in virology, containment techniques and procedures to fulfil his/her duties. It is to be expected that he/she would also have a broad based knowledge of the FMDV with particular respect to its physico-chemical properties, mode of transmission and other topics of relevance to his/her role.
   (f) The BRO should review regularly both technical reports concerning the various containment facilities as well as data relating to their day to day operation and

monitoring. On the basis of such information, the officer should inform senior management of any concerns he/ she may have and as they arrive as well as prepare an annual report on all relevant containment elements of the facilities.

6. *Accessibility to live FMDV*: Access to live FMDV should be limited to adequately instructed key personnel authorised by the management.
7. *Record keeping:* Detailed records of handling live FMDV (e.g. virus strains and dates used) should be kept and stored at least 5 years. Inventory lists including information on the location where a virus strain is stored should be maintained and periodically inspected and crosschecked. Laboratory books or other daily records of procedures by staff working with FMDV should be in place to enable retrospective analysis of activities for at least 12 months.
8. *Accident / incident reporting system*: Each facility should have an accident / incident reporting system in place, with a procedure for rating of the risk of the event and a decision making process for recording, reporting and remedial actions. An example of a risk rating system and associated decision tool is given in ANNEX I.
9. *Accident / Incident review system*: there should be a system in place to ensure each incident/accident is reviewed to ensure that the lessons learned have been identified, the type of failing in control measures is recognised, and adequate and proportionate remedial measures set in place. A statistic concerning accidents / incidents should be made available to the management at least annually.
10. *Systems to review biorisk changes*: changes to the design, operation and maintenance of a facility including biosafety / biosecurity procedures and risk assessment should be reviewed, verified, approved and documented through a formal change control process before implementation. Trigger points for review or drafting of new risk assessments should be identified.
11. *Emergency management plans* (contingency plans): types of emergency should be identified, including fire, flooding, loss of essential services, security breaches and major events affecting integrity of buildings, and standard management procedures for each event developed, documented and made permanently available to staff.
12. *Access to site:* management should implement and document a system for controlling access to areas of the site where the activities of the area pose a potential hazard. There should be physical security measures to restrict access.

    Management should define the different zones on the site, taking into consideration the hierarchy of risk of activities in each zone. A suggested typology is:

RED	*[=Restricted Zone = where FMDV is manipulated and/or which contain infected animals]*
ORANGE	*[= support services and access to the Restricted Zone]*
GREEN	*[general access and administration].*

RED, ORANGE and GREEN zones are situated within the *Controlled Zone* = area within the outer security barrier or fence of the facility.

The minimum requirements are to clearly define and document the zones under control of the BRO, including definition of the outer perimeter of the site, lower risk areas for personnel and plant access, the location and barriers of the laboratories in which FMDV is handled, and the location and access points to waste treatment (including ventilation systems).

II. Training

13. The organisation should ensure that personnel are competent for their designated roles and receive appropriate training on a regular basis. In particular, training requirements and procedures for biosafety and biosecurity related training of personnel should be identified (training programme) and established (training manual) and training records should be maintained.

14. Training content and training tools should be defined taking into account the different target audiences and the individual learning differences within a facility. Training efficacy assessment should be considered wherever possible and appropriate. Training should be reviewed on a regular basis.

    The BRO should be in charge of providing information and advice on biosafety and biosecurity to laboratory staff, cleaning personnel, visitors, contractors as well as to other persons working either in locations in which FMD is handled or adjacent facilities such as service areas. Personnel should be made aware of the responsibilities, the specific containment features and the risks associated with such activities.

15. Training should be provided on the specific properties of FMD, the primary and secondary containment features and the biosafety / biosecurity procedures pertinent to each facility.

16. All staff members must be appropriately informed and regularly trained in emergency evacuation procedures with special attention being given to security requirements in cases of fire.

III. Laboratory Biosecurity

Note: Additional considerations and notes are given in ANNEX I.

The objective of Laboratory biosecurity is to protect biological materials containing FMD virus against deliberate removal from the facility.

17. It is part of the duty of care of every facility handling FMDV to ensure that it minimizes the risk of virus misappropriation by intruders and people with access rights to the facility, through measures taken following a *formal threat assessment process*.

    In a threat assessment the critical assets of a facility should be identified and the facilities' vulnerability to threats should be assessed. Any decision not to undertake such an assessment requires documentation and justification. Based on the threat assessment, structural (e.g. building design, IT etc.), physical (cameras, fences, access etc.) and organisational (security policy, accessibility etc.) measures should be taken.

18. To comply with point 17, the minimum requirements are*:*

    (a) *Security system* that is appropriate to detect and alert security to the presence of intruders, with a security plan in place for rapid response to intrusion.

    (b) E*ntry Recording system:* Access to the facility should be recorded to provide an audit trail of who was in the facility at any given time.

19. *Threat reduction/control measures*: Due to the unpredictability of the actual threat, controls are required to reduce the risk to an acceptable level. These controls should consider structural, physical and organisational measures and must address at least the following scenarios:

    - Intruder attempting to remove FMDV from the facility by forced or fraudulent entry;
    - Staff member removing FMDV from the facility;
    - Shipment of virus containing materials.

IV. Personnel

20. Control of entry into and exit from the Restricted Zone must take place only through changing and showering facilities. This means a complete change from private or controlled area working clothes to dedicated Restricted Zone working clothes on entry and the reverse process on exit but with a shower before leaving the Restricted Zone.

21. A code of FMDV containment practice, including instructions for entry into and exit from Control Zones/Restricted Zones, must be available for all employees and visitors on site.

22. The FMDV containment rules and other relevant documents provided by the management must have been read and signed by each employee at the beginning of their employment. At this time, it should also be made clear to new staff that any violation of such and similar regulations may result in disciplinary actions by the management and the terms of employment should indicate this.

23. *Control of access to Controlled zones and critical areas*: A level of security checks is recommended for all individuals with access to FMDV laboratories or critical plant/service areas of these laboratories. The performance of such checks will depend on the legislation of the country and procedures should have been developed in consultation with the police and relevant government agencies of the country.

    Access to FMDV containing materials in the laboratory should be restricted to trained and dedicated staff on the basis of legitimate needs. The number of individuals with access to virus storage areas should be kept as small as reasonably possible.

24. *Visitors*: There must be rules in place governing the access to controlled zones by visitors, covering at least the record keeping and the possible use of background checks. The security system should verify the identity of visitors through use of unique identifiers including passport or ID card details. The reasons for each visit and the responsible person must be recorded.

25. Visitors have to be instructed in the specific containment procedures (eg. decontamination) of each facility before entering the Controlled / Restricted Zones. There must be a system in place that guarantees that these procedures are properly followed.

26. *Oversight (mentoring)*: A system for oversight of new personnel should be established, such that all new staff has someone assigned for oversight who has sufficient understanding of the biosafety rules.

27. The human resources department should establish procedures to support compliance with biorisk management procedures. At the work place, factors which might

compromise compliance are e.g. excess work load, bullying, bad management style or lack of oversight. Also on the level of individual employees, problems like substance abuse or mental conditions could compromise compliance with biorisk management rules.

28. Quarantine: each facility must define and apply quarantine periods for persons authorised to work in each category of Controlled Zone, to reduce the risk that personnel will cause a release of FMD virus as a result of virus carriage on their body. A range of quarantine periods may be defined depending on the level of exposure to virus. Depending on the risk assessment quarantine rules may be applied to other areas of a facility as well. For the Green Zone, usually no quarantine period is necessary.

    Persons, including visitors, authorised to enter the Restricted Zone must agree not to keep any animals which are susceptible to FMD, nor reside on premises where such animals are kept and to abide by minimum standards of quarantine, i.e. no contact with animals susceptible to foot-and-mouth disease for at least three days.

29. Personal protective equipment; regular supply of appropriate laboratory clothing for use within the Restricted Zone.

V. Facility Design

30. General construction of buildings and their surfaces, including ducting of the air conditioning system:
    - maintain inward flow of air through doorways and other openings at all times
    - properly maintained condition with a high standard of airtightness
    - insect, rodent and bird proof.
31. Windows:
    - Sealed, toughened and preferably double glazed, and able to withstand operating pressures and all but major impact.
    - Equivalent standard in animal rooms and at a height where animals are not able to break.
32. Doors:
    - warning signs at entrances:

      ACCESS FOR AUTHORISED PERSONNEL ONLY

      BIOLOGICAL HAZARD

    - access restricted by locked doors where locks are operated from the outside. The advantages of a key-less lock system centrally controlled by the biosafety department should be explored that prevents unauthorised cutting of falsified spare keys and allows the biosafety department to reset access rights as necessary.
    - airlocks provided with airtight doors which are interlocked to prevent opening of both doors simultaneously, in particular following a gaseous decontamination cycle;
    - doors should be fitted with windows to allow staff outside of a room to see actions inside and provide assistance if necessary.

33. Walls, floors, ceilings:

    – In many respects, the surfaces and material appropriate to Pharmaceutical facilities respecting GMP standards are also relevant to laboratories handling FMD virus. Notably, surfaces should be impervious, smooth, crevice free and easily cleaned and disinfected. Cavities within the fabric of the facility should be avoided (e.g cavity walls) unless all penetrations of the walls, floors and ceilings are thoroughly sealed with suitable materials such as silicone mastic. Crevices and joins between surfaces should also be sealed with similar materials. Continuity of seal should be maintained between floors and walls. A continuous cove floor finish up the wall is recommended in particular for areas where major spillages will occur, e.g. animal and post mortem rooms.

    – Sealed (airtight) entry of service lines.

34. *Communication*: All areas equipped with telephones and, in some areas, cameras, to ensure additional security outside of normal operations and allow staff to report issues including accidents and incidents without leaving work area.

35. *Emergency back-up power*: The laboratory facility should be equipped with a back-up source of electricity (an emergency generator) which starts with a delay of no more than a few minutes in the event of power failure. Alternatively, it is acceptable if the commercial power supplier is able to guarantee a supply from an alternative source within a few minutes of the main power failure. The delay period that is permissible will depend on the airtightness of the key buildings in the facility where virus in aerosol form may be present. In the design of a Restricted Zone facility, special attention should be paid to the critical electrical supply circuits such as air handling systems, cold stores, safety cabinets, and other equipment and installations relating to the security and safety of the facility. There should be no possibility of the emergency supply being diverted from critical circuits by less important demand from non-critical equipment. Thus, the critical supply circuits would include air handling systems, cold stores, safety cabinets and other equipment and installations relating to security and safety of the facility.

VI. Handling of FMD virus

36. *Recording receipt of virus containing materials*: A system should be in place for recording receipt of specimens or samples known or reasonably be suspected (to contain FMDV. The accompanying type and strain identification, or such information generated by the laboratory, respectively, should be recorded.

37. Except in cases when this is not technically feasible (e.g. during large animal experiments and post-mortem examinations), materials known or expected to contain FMD virus must either be kept within closed vessels or in devices that in combination with suitable operating procedures will function as primary containment. Such devices should be equipped with suitable filters, for example HEPA filters for which the requirements are defined in the Glossary, or equivalent off-gas or vent filters (primary containment). A suitable disinfectant should be kept close to the work areas such that a spillage can be rapidly dealt with.

38. In areas where only small quantities of virus are handled (10 litres or less of cell culture), liquids and suspensions containing FMDV should be inactivated by a

validated procedure, for example, dilution in disinfectants, before disposal into the liquid waste system of the facility.

39. When large quantities of virus are processed (e.g. for vaccine production), it is necessary to transfer virus with a contained system of vessels, pipes and other equipment. To permit fluid transfers, air needs to enter and exit equipment and infectivity must be efficiently removed by a suitably validated procedure. Usually, this is done by filtration and a number of manufacturers supply filters capable of removing FMD virus with very high levels of efficiency. Procedures are also required for decontamination of vessels, pipes and other equipment after the process has finished and before the process is either repeated or items are opened or stripped down for cleaning or maintenance. Usually this will require a chemical decontamination stage followed by steam sterilization.

40. Inoculation of animals, maintenance of infected animals and post-mortem examinations must take place within the Restricted Zone in rooms (normally dedicated animal or post-mortem rooms, respectively) that in combination with suitable operating procedures function as a primary containment. [see glossary] Personnel must wear appropriate and comprehensive protective clothing to minimise exposure of body surfaces to virus splashes and aerosols when handling virus suspensions and when inoculating or handling infected animals. On exit from an animal and post-mortem rooms, protective clothes and footwear must be left inside these rooms or in ante-rooms to these rooms. Showering and complete change of clothes is required before the operator can move to an area not operating under a negative pressure/air filtration system.

41. Movement of materials known or expected to contain FMD virus out of one zone (eg laboratory), to another zone (e.g. animal rooms) on the same site must be governed and made by a set of procedures that prevent possible loss or spillage of virus in a non-Restricted Zone of the facility. As a minimum requirement, such materials are transported between the zones within a leak and break proof container. Staff making such transfers should be fully authorised to do so and be familiar with the emergency response procedures in the event of accident or incident.

42. Laboratory facilities and equipment must be cleaned and appropriately disinfected at regular intervals. In particular, benches and other flat surfaces exposed to virus should be wiped down with a suitable disinfectant as soon as open work has finished.

VII. Air Handling – Live Virus Facilities

Note: Additional considerations and notes are given in ANNEX I.

Ventilation systems

43. *Negative pressure ventilation system*: All facilities used for the handling of FMDV must operate under a negative pressure ventilation system with HEPA filtration of exhaust air and systems to prevent air escape on the inlet supply.

    In areas where only small quantities of virus are handled (10 litres or less of cell culture), the minimum negative pressure should be 35 Pa [1]but due consideration needs to be given to ensure a gradient from the periphery of the Restricted Zone to the area

[1] **1 pascal (Pa) ≡ 1 N/m^2 ≡ 1 J/m^3 ≡ 1 kg/(m·s^2) ≡ 0.102 mm water column**

where virus is handled. From a practical perspective, it is difficult to achieve gradient steps of less than 10 Pa and this will tend to dictate the choice of pressure in the most negative part of the Restricted Zone. For areas where larger quantities of virus are handled such as large scale virus production rooms and large animal rooms, the minimum negative pressure should be 50 Pa. A system should be in place to prevent a positive pressure occurring within the building due failures or faults within the Restricted Zone ventilation system.

44. *Exhaust air filtration system*:

Laboratories:	Double HEPA (H13 or H14) filtration of exhaust air. Use of a single HEPA filter may be acceptable, provided that it is demonstrated that open work with live virus is at all times restricted to within biological safety cabinets (BSC) which have HEPA filtration of exhaust air, thereby maintaining an effective double HEPA filtration following open work.
Animal rooms	Double HEPA filtration of exhaust air is obligatory.

Production laboratories: Double HEPA filtration of exhaust air is obligatory.

45. *Inlet air supply*: A system must be in place to prevent escape of air via the inlet in case of ventilation shut-down. This may be achieved by a single HEPA filter or automatic dampers in the air inlet system.

46. The air pressures within the different rooms of a Restricted Zone should be continuously monitored by manometers and a system must be in place so that staff working in these areas are informed if significant loss of air pressure occurs and the actions to be taken. Manometers should be labelled to indicate the working pressure and the minimum and maximum limits within which open virus work is permitted. Under any of these alarm conditions, the primary action is to cease all open virus work and secure the workplace by sealing virus containers and disinfection of surfaces and protective clothing. The opening of doors leading to the contained area or to rooms containing infected animals or carcasses should be avoided as far as possible until the pressure difference has been restored.

47. All critical filters (HEPA) should be incorporated into a preventative maintenance programme. In particular, the efficiency of HEPA filters should be checked at least once per year, and in line with requirements of EN 14644.

48. When HEPA filters are installed or replaced, an in-situ efficiency test must be carried out by trained personnel with validated equipment. Replacement of HEPA filters must be performed in accordance with an authorised procedure. Strict precautions must be taken to prevent the spread of virus with used filters or contaminated air. Replacement of filters from outside the Restricted Zone must take place after decontamination "in situ" or in "safe change" air-handling units. Filter specifications and test results supplied by the manufacturer should be incorporated into the maintenance records but cannot replace in-situ testing because filters may have been damaged during transportation or may not have been fitted into the gaskets properly during installation.

49. Filters must be changed when the pressure difference exceeds certain limits in accordance with the instructions given by the manufacturer, or sooner if the filter fails one of the prescribed efficiency tests. Additionally, it may be necessary to change some filters more frequently if they are subject to high humidity or high particle challenge.

50. Animal rooms – prefilters should be designed in a way that they can be changed without shut-down of the ventilation system.

51. HEPA filters in safety cabinets should also be checked at least once per year. Movement of safety cabinets should be accompanied by re-validation of the filter integrity due to possible flexing and movement on the filter cartridge or filter housing.

52. Off-gas or vent filters require testing on installation and at least once per year.

VIII. Waste management

Effluent

53. Effluent from Restricted Zone laboratories and from facilities holding FMD infected or potentially infected animals must be treated in a manner which ensures that there is no residual infectivity in the effluent using a suitable validated procedure. Both heat and chemical treatment may be used to process the effluent provided all of the material in the effluent is exposed to the specific treatment.

54. The treatment must be validated for the highest virus load and the most difficult matrix that can reasonably be expected. The possibility that virus particles may be protected from inactivation by proteins or lipids, and/or by aggregation or precipitation, must be taken into account in the validation process.

55. The entire effluent treatment system must comply with high containment conditions. In every case it must be ensured that no leakage from the primary containment system into the environment can occur.

56. There must be sufficient storage capacity (tanks) for the storage of untreated effluent.

57. The equipment must have automatic monitoring systems to ensure proper function. These systems must ensure that the required conditions for inactivation of FMDV have been reached before the effluent is discharged. The systems should be continuously monitored and all critical data recorded. The system should be designed in a way that in case of any failure, the likelihood of a release of potentially infectious material is minimised.

58. Treatment options:

    Heat treatment: FMD virus is quite sensitive to heat at 100°C for 1 hour or an equivalent heat effect has been shown to be sufficient to inactivate FMDV in effluent to the extent that no residual infectivity can be detected. The treatment process should be monitored by multiple, automatic and continuous time and temperature measurements, combined with automatic measurement of flow rates or volumes. Any treatment system must ensure homogeneity of the effluent during the inactivation process. All data relevant to the inactivation process and the release of effluent must be recorded. Critical data measuring and logging equipment must be validated by qualified personnel at least annually.

    Chemical treatment: FMD virus is quite sensitive to acid and alkaline pH conditions. NaOH or Na_2CO_3 or other alkaline treatment at pH 12 for at least 10 hours has been shown to be sufficient to inactivate FMDV in effluent and are particularly effective because of their action on concentrated biological effluents. As with heat, thorough mixing of the materials must be ensured. The treatment process should be monitored by multiple, automatic and continuous time and pH measurements. After treatment, the

materials must be neutralized and the pH checked before the effluent is released. All data relevant to the inactivation process and the release of effluent must be recorded. Critical data measuring and logging equipment must be validated by qualified personnel at least annually.

Solid waste (animal carcasses, feedstuffs, laboratory waste etc.)

59. The principle requirement is on-site inactivation of FMDV in waste using a validated method.

60. These methods include:

- Sterilisation by steam using an autoclave (at least 115°C for 30 minutes or equivalent heat effect). It is essential that the different autoclave load types (eg plastic waste, paper waste, waste liquids) are each validated for the maximum load size with suitable recording devices, e.g. thermocouples, at different locations within the load including the centre of the load. Typically, autoclave periods are 30 min or more. Autoclaves should be double-ended so that treated waste does not need to re-enter the Restricted Zone. Autoclaves should be revalidated at least annually by experienced personnel. Depending on the national requirements, it may be necessary to dispose of the autoclaved waste by incineration on or off the site.

  Rendering of carcasses on site, in compliance with the requirements for category 1 animal by-products (Regulation (EC) No 1069/2009 and Regulation (EC) 142/2011).

- Incineration on site. The incinerators must comply with current safety standards and be fitted with afterburners.

61. *Emergency procedures*: A similar level of safety must be demonstrated for procedures used when normal waste treatment procedures can not be followed, e.g. because of a breakdown of equipment. Emergency procedures must be documented in the laboratory emergency plans, and include procedures for storage until treatment and final disposal.

IX. Equipment and Materials

Laboratory fittings

62. *Benches* shall be smooth, impervious and resistant for any chemicals used in the facility. Junction between horizontal and vertical surfaces should be radiused.

63. *Centrifuges, sonicators, homogenizers and other equipment* must be designed so as to contain aerosols or be used within safety cabinets where any aerosols generated will not escape to the atmosphere of the restricted laboratory.

Removal of equipment and other material

64. Before removal from Restricted Zones, equipment must be decontaminated according to the size and use of the equipment:

- either by steam sterilization within an autoclave, at 115°C for 30 minutes, or an equivalent heat effect, or

- after surface disinfection, fumigation with formaldehyde (10 g/m3 at 70 % RH) for at least 10 minutes or (3 g/m3 for 24 hours or equivalent with other aldehydes, e.g. glutaraldehyde, or ethylene oxide (0.8 g/litre at 50°C for 1.5 hours). Equipment, for example contractors' tool boxes, laptops, etc. which is fumigated out of a Restricted

Zone should be cleaned and be opened as much as reasonably possible to allow penetration of the gaseous fumigant; or

– thorough washing in an appropriate chemical disinfectant[2] such as:
  - 4 % Sodium Carbonate or 10% washing soda (Na_2CO_3 Dehydrate);
  - 0.5 % caustic soda (NaOH);
  - 0.2 % citric acid;
  - 4 % formaldehyde or equivalent with other aldehydes, e.g. glutaraldehyde; or
– an equivalent disinfection protocol officially approved for the purpose.

65. Decontamination of clothing before removal from the Restricted Zone for laundry must include a wet heat treatment step (autoclaving at a temperature of at least 115°C for 30 min, or equivalent heat effect). A laundry process without autoclavation is permitted if performed on-site in a double-ended pass-through laundry device. Such a laundry process must include a validated alternative inactivation step.
66. Documents should be sent out of the Restricted Zone preferably in electronic format (fax, scans, electronic documents, e-mails etc.). In case papers have to be taken out of the Restricted Zone, they must be treated by a validated procedure e.g. autoclaving, irradiation or ethylene oxide treatment. In cases when only low levels of contamination can reasonably be expected and following risk assessment, paper can be sealed and kept at > 20 ^{0}C for two years before being taken out of the Restricted Zone.

Removal of biological material from the Restricted Zone

67. Before sending non-FMD biological material to another laboratory which lacks the required level of containment, the necessary precautions must be taken to ensure that the material does not contain FMDV.

    Thus if the source of the biological material is a restricted laboratory area, it is essential that it is subject to an innocuity test to demonstrate freedom from FMDV or a validated treatment that destroys FMDV infectivity.

    The recipient laboratory must be informed about the potential risk of material coming from a laboratory manipulating FMDV. The recipient laboratory must further sign a statement that it is prepared to receive the material and that it will take the necessary precautions.
68. For the shipment of FMDV containing materials to other laboratories an innocuity test is not required if the material is sent to a high containment laboratory licensed to handle live FMDV.

    The laboratory which provides FMDV to another laboratory has a duty of care to ensure that the recipient laboratory is authorised to handle FMDV. Before shipment, it has to ask for a statement from the recipient laboratory that it is requesting the virus only for legitimate purposes and will not redistribute the virus to other laboratories

[2] *Note:* The efficiency of these chemical disinfectants is considerably improved by the addition of a non-ionic detergent.

without written consent. The sending of materials containing FMDV is subject to international requirements governing transportation.

X. Decommissioning containment compartments for maintenance or renovation purposes.

Note: Additional considerations and notes are given in Annex I.

69. Maintenance or renovation work that may compromise the integrity of the containment barrier thus possibly allowing the escape of air or liquids must be preceded by an assessment of the risk and a safety plan.

70. Decontamination of rooms/compartments, to reduce the risks to an acceptable level, are required before these can be decommissioned permanently or temporarily, for example during renovation.

    Standard Treatment procedures include fumigation with formaldehyde after making the room effectively air-tight.

71. Waste building materials generated by demolition and redevelopment and other potentially contaminated materials must be treated in a way that any residual infectivity is inactivated. If autoclaving is not feasible, it should be sprayed or fumigated to disinfect surfaces, and then stored on site for 6 months before removal.

Glossary

Terms are in line with the proposed "Laboratory Biorisk Management Standard" (CEN draft document for public comment, 2007-07-25)

Biorisk (adapted from OHSAS 18001:2007): combination of the likelihood of the occurrence of an adverse event involving exposure to biological agents and toxins and the consequence (in terms of accidental infection, toxicity or allergy or unauthorised access, loss, theft, misuse, diversion or release of biological agents or VBMs) of such an exposure.

Biorisk officer (BRO) or biorisk advisor (Biosafety / Biosecurity Officer): a staff member of an institution who has expertise in the biohazards encountered in the organisation and is competent to advise top management and staff on biorisk management issues.

Biosafety (adapted from: WHO/CDS/EPR/2006.6): Laboratory biosafety describes the containment principles, technologies and practices that are implemented to prevent the unintentional exposure to biological agents and toxins, or their accidental release.

Biosecurity (adapted from: WHO/CDS/EPR/2006.6): Laboratory biosecurity describes the protection, control and accountability for valuable biological materials within laboratories, in order to prevent their loss, theft, misuse, diversion of, unauthorised access, or intentional release.

Restricted Zone: area of the facility where FMDV or diagnostic samples submitted for FMD testing is manipulated and/or which contain infected animals, bounded by physical barriers to prevent air and fluid escape except through air filtration and waste treatment systems.

Controlled Zone: area within the outer security barrier or fence of the facility, containing the Restricted Zone, the services for the Restricted Zone, and zones for access and administration.

Open virus work, or open work: describes the handling of materials containing FMDV (usually liquids) in which exposure to room air occurs, for example during the pipetting of liquids into containers, and the subsequent exposure of the liquid handling object (pipettes etc) to air.

Primary containment: measures that contain the live virus at source, within closed containers or within a class I, II or III microbiological safety cabinet, or for animals, by physical containment in specially constructed rooms with treatment of all waste including the HEPA filtration of air.

HEPA filter: High Efficiency Particulate Air filter: the classification of HEPA filters is on the basis of efficiency of removal of the most penetrating particle size, and set by international standards (EN1822). In the context of this minimum standard, all HEPA filters must at least meet H13 requirements. However in order to increase the margin of safety, H14 filters are recommended.

HEPA filter performance requirements are defined by EN1822; to classify as H13, the filter must remove > 99.95% of particles of the most penetrating particle size (~0.15 μm). A leak is defined as penetration > 5 times the required integral efficiency, i.e. 5 times 0.05% = 0.25%. To classify as H14, the filter must remove > 99.995% of particles of the most penetrating particle size (~0.15 μm). A leak is defined as penetration > 5 times the required integral efficiency, i.e. 5 times 0.005% = 0.025%.

ANNEX I

Additional Considerations and Examples

I: Establishing an FMD incident risk rating system

Each facility should establish a risk rating system and an associated set of incident management procedures, including reporting and responsibilities in the event that a high risk incident occurs.

Risk is the product of consequence and likelihood. The consequence of an FMD escape into susceptible livestock (resulting in an outbreak) is huge.

In establishing a risk rating system, the following factors should be considered:

– Where does the incident occur? (for example in an animal room)

– What type of event? (for example a visitor leaving without showering)

– How much potential virus exposure or loss? (for example number of persons, time or volume)

– To where was the virus release? (for example outside of the high containment area, to ruminants, to areas within the perimeter of the facility).

Each facility should establish their own risk rating system, taking into consideration e.g. the history of incidents, estimations of likelihood, objective data, and computer simulations. The risk rating system and reporting requirements should be agreed at the level of the top management of the facility, and reviewed on a regular basis.

Once established, the risk rating system can be used in training of staff on their reporting requirements, setting out the types of event or that should be reported to the line manager and/or biorisk officer.

Example of a risk rating system

Where		**What**		**How much***		**To where**	
5	Animal room containing FMD infected pigs.	**5**	Potentially contaminated person, without showering	**5**	Unknown or very high or long time: > 1 L or Kg fluid or material/day. >10 days air. > 50 persons.	**5**	Outside containment, probable exposure of FMD susceptible animals.
4	Animal room containing FMD infected animals (not pigs).	**4**	Potentially contaminated waste.	**4**	High: 10 – 100 ml or gram fluid of material / day. 1 – 10 days leakage of air. 5 – 50 persons.	**4**	Outside containment, to Yard or farm with FMD susceptible animals. In contact with other (not FMD) Vet.Bios.Level 3 and 4 susceptible animals.
3	Lab undertaking FMD virus work Or During the first half of the FMDV disinfection process of formaldehyde or steam autoclaves or EthyleneOxide sterilizers.	**3**	Potentially contaminated air. Or Potentially contaminated person, after showering	**3**	Moderate: 1 – 10 ml or gram fluid or material / day. 1 – 24 hour leakage of air. 2 – 5 persons.	**3**	Outside containment, to NON FMD susceptible animals
2	Lab not handling FMD virus but within common building/containment to labs handling FMDV Or During the second half of the FMDV disinfection process of formaldehyde or steam autoclaves or Ethylene Oxide sterilizer.	**2**	Potentially contaminated fluid.	**2**	Little: < 1 ml or gram fluid or material / day. <1 hour leakage of air. 1 person.	**2**	Outside high containment suite but on terrain of the institute
1	In engineering maintenance areas – HEPA filter replacement, etc	**1**	Other Potentially contaminated items	**1**	Very little << 1 ml or gram fluid or material / day. <<1 hour leakage of air.	**1**	In engineering maintenance areas – HEPA filter replacement, etc

* temperature, humidity, expired time will also have influence on this issue

Relative risk = where x what x how much x to where

Example

A person who was working in the laboratory where live FMD is handled was observed to pass to the area outside of high containment, without taking a shower, but did not leave the perimeter of the facility.

Risk rating: 3 x 5 x 2 x 2 = 60

relative risk	**≤20 is 'Acceptable'**	**21 – 60 is 'Low'**	**61 – 250 is 'Substantial'**	**>250 is 'Catastrophic'**
decisions	Report Biorisk Officer.	Report Biorisk Officer. Report Biorisk Committee. Report General Manager.	Report Biorisk Officer. Report Biorisk Committee. Report General Manager. Call together Crisis Team. Decision about the necessity to inform authorities.	Report Biorisk Officer. Report Biorisk Committee. Report General Manager. Call together Crisis Team. Report to Regulatory autority/Chief Vet. Officer

II: Improvement of biorisk management through analysis of incidents

Management should take a high interest in learning from reported incidents. Each may be considered a form of failure or non-conformity to the expected performance of the risk control measures, and occur as a result of failure in the engineering controls and/or personnel related control measures.

The cause of each event may be categorised as:

Related to engineering:

– hardware (as facilities and equipment)

– design (as irrational lay-out and ergonomics)

– maintenance (as planning and availability)

– procedures (as standard operations and relevance)

– defences (as protective equipment and signals).

Related to personnel management:

– error-enforcing conditions (as occupational health and attitude)

– housekeeping (as tidiness and discipline)

– incompatible goals (as costs and safety)

– communication (as interpretation and point of time)

– organization (as responsibilities and authority)

– training (as knowledge and experience).

III: Threat assessment

In deciding upon undertaking a threat assessment, the following should be considered:

1. The threat of criminal use of FMDV for any malicious purpose has to be carefully assessed to determine the additional risk that arises from operating FMDV facilities. FMDV laboratories have exclusively peaceful objectives concerned with development and implementation of control measures. They are critical for the technical cooperation with veterinary services around the world in order to minimize the economic impact of FMD on livestock and economies. The threat of criminal use of FMDV is subject to major change as the political agenda of terrorist group changes.

2. The threat and consequences of a terrorist attack will vary by country. Because of the transboundary nature of FMD, there is also the possibility that a deliberate release may occur in another, possibly neighbouring, country. For this reason, effective control measures need to be consistently applied throughout all EU member states that operate FMD laboratories. As the motivation for a deliberate release may change unpredictably over a very short period, effective control measures need to be sustained at all times and be sufficiently flexible to allow an enhanced response if required.

   Facilities permitted to handle FMDV are obliged to prevent illegal access and removal of the virus. As a consequence, such access to laboratory-held virus must be substantially more difficult than acquiring the virus in the field.

Threat reduction/control measures: due to the unpredictability of the actual threat, controls are required to reduce the risk to an acceptable level. These controls should consider structural, physical and organisational measures and must address the following:

3. Intruder attempting to remove FMDV from the facility by forced or fraudulent entry.

   Appropriate controls include 1) physical security measures restricting access to authorised staff and contingency plans in the event of intrusion, 2) secure storage of virus containing materials including maintenance of inventories of stocks.

4. Staff member removing FMDV from the facility

   Appropriate controls include 1) vetting of persons before authorisation of access, and escorts for persons allowed temporary access when security clearance is not available; 2) restricted access to FMDV virus material in the lab to trusted staff on the basis of a legitimate need, 3) access to the facility is logged [and records maintained for at least two years] to provide an audit trail of who was in the facility at any given time. 4) Design of the laboratory or facility such that the number of staff needing to enter the secure areas is limited. Eg some engineering aspects of the design of the facility can be arranged so that certain services can be maintained from outside of the security envelope.

5. Shipment of virus containing materials

   Appropriate controls include standard procedures before authorisation, including receipt of adequate information from the intended recipient of its authority to handle FMDV, and written agreement that the recipient laboratory will not redistribute the virus to other laboratories without applying the same risk assessment and will adhere to relevant national or international legislation relating to shipment and supply of dangerous animal pathogens.

IV: Air-handling

1. Depending on the small animal species, route and nature of infection and method of animal containment and handling, quite high titres of virus in relatively uncontrolled conditions might be produced. Consideration should be given to the appropriate negative air pressure requirements, with 35 *pascal* negative pressure as the minimum.

2. Provisions must be in place to ensure that in the Restricted Zone no overpressure is generated. One approach is to interlock the inlet and extract fans so that the most that can occur is that the air supply and extract fails and the negative envelope decays solely depending on the airtightness of the building. An emergency back-up extract fan is recommended so that the negative envelope can be restored in the event of the main extract fan failing and this also should be interlocked to the supply fan to avoid very high negative pressures which may cause damage to the fabric of the building. As an alternative, the air extraction plant can be divided into several parallel sections so that the negative pressure can be maintained if one section fails or is shut down.

3. It is advisable to have and maintain other filters within the air handling system, notably, prefilters upstream of the HEPA filters. These other filters will conserve the life of the HEPA filters and reduce the need to change at the annual

maintenance interval. In properly maintained systems, it is relatively rare to change the terminal extract filter due to the efficiency of particulate removal by all of the filters upstream. However, high levels of humidity will shorten the life expectancy of filters and large amounts of dust generated by nearby building works or other activities will soon blind filters even with efficient prefilters upstream.

4. Off-gas or vent filters: This type of filter is often steam sterilised and filter efficiency testing involves different approaches such as the water intrusion test. At the smaller scale, disposal cartridge filters may be appropriate as vent filters to allow gas exchange while preventing virus escape from the container to the laboratory environment.

5. Although not widely used, sterilisation of extract air may be done by heating the air as it passes through an in-line furnace.

6. To save energy, air extracted from a Restricted Zone may be partially recirculated into the same Restricted Zone provided it passed through a HEPA filter before it re-enters the laboratory. However, the advisability of recirculation and the proportion of air recirculated will need to be considered against the quality of the air leaving and re-entering the work place and the activities within the workplace.

7. In the event that HEPA filters become blocked prematurely (ie prior to annual testing), this does not normally represent a problem in terms of the integrity of the affected filter(s), but it probable that the increased resistance to airflow and consequent problems of balancing the pressures in the different rooms of the Restricted Zone will necessitate changing the affected filters.

V: Decontamination of compartments:

The compartment must be made airtight to make fumigating possible, if necessary by means of temporary panels.

Formaldehyde procedure:

1. Check the compartment and accompanying drawings for connections with containment facilities that must be closed. Close down utilities as gas, water, electricity, sewerage, steam and if possible ventilation.

2. Empty the compartment, for example by moving objects to other containment facilities. Remove porous material. Discard material via validated procedures like autoclaves and formaldehyde airlocks. Open non removable installation parts to make them accessible to vapour.

3. Clean the compartment and disinfect critical points which are possibly contaminated.

4. Prepare the fumigating equipment and shut the compartment airtight.

5. Disinfect (air)ducts and HEPA filters for example separately by injecting formalin.

   Use a fumigating method in conformance with a validated procedure used for formaldehyde airlocks.

Use bioindicators, (preferably a rapid bioindicator system) to prove the efficacy of the fumigating process.

Set restrictions for access such as clothing, quarantine for people and demolition material, in order to be able to make corrections in case of accidents.

6. Inspect the maintenance and renovation activities to be performed in the compartment.

SECTION II. MINIMUM STANDARDS OF BIORISK MANAGEMENT FOR LABORATORIES UNDERTAKING DIAGNOSTIC INVESTIGATIONS FOR FMD IN THE FRAMEWORK OF A NATIONAL CONTINGENCY PLAN

(MBRM STANDARDS FOR FMD CONTINGENCY LABORATORIES)

Introduction

The following Minimum Standards for laboratories undertaking diagnostic investigations, refers to the laboratories mentioned in Annex XV to Council Directive 2003/85/EC which are designated by the competent authorities as "national laboratories" or in point 13 of Annex XV as "other laboratories" that would be licensed to undertake diagnostic tests as part of national contingency plans but only test field samples originating from the country where the laboratory is situated by assays which do not contain or require live FMD virus as reagents or controls and which do not amplify infective virus. Such "FMD Contingency Laboratories" must operate to standards that will result in inactivation of live virus if received in samples. During an outbreak, they may offer significant advantages in respect to speed and sample throughput as the number of laboratories fully meeting the "MBRM Standards for FMDV Laboratories" is very limited. In some "FMD Contingency Laboratories", rooms equipped with an air handling system providing HEPA filtration of exhaust air may be available for the most critical activities.

Real-time PCR has been introduced in many laboratories, e.g. regional veterinary laboratories. While the inactivation treatment prior to PCR in principle may be carried out on the suspect premises, there currently is no validated and fully satisfactory procedure that could be used for this purpose and thus opening the vessels containing potentially infectious material in a class II microbiological safety cabinet followed immediately by inactivation is considered a suitable alternative.

Furthermore, a national competent authority may decide to authorize a "FMD Contingency Laboratory" to test non-inactivated samples by antigen ELISA in order to allow these labs to confirm PCR results, maintain a back-up method in case PCR fails and to determine the serotype although this procedure poses a higher risk. The use of a lateral flow device (LFD), either on the premise or in a "FMD Contingency Lab" in a MSC, is an alternative to antigen ELISA that poses a lower risk but currently does not allow serotyping.

Serology by commercially produced FMDV-ELISA kits can be performed in many laboratories, e.g. regional veterinary laboratories, which can process samples with a high throughput. In case of an outbreak, this allows to increase the throughput of diagnostic samples significantly, which will often be a crucial factor for successful disease control and timely recovery of the previously free status. Serological samples should be opened and processed in a way that the generation of potentially infectious aerosols is minimized and air that might contain such aerosols should be released through a HEPA filter as far as possible.

While due to the dynamic nature of an FMD epidemic also samples coming from holdings without clinical signs may occasionally contain virus, samples for holdings with clinical signs suggesting the presence of FMD represent a higher risk and should be handled with special caution.

Packaging of samples

Samples must be put into watertight primary containers (e.g. plastic tubes) and the primary containers must be packed in watertight secondary packaging, which should be a strong crushproof and leak-proof container, with absorbent material that can absorb the entire contents of all the primary containers. The packaging process must include a disinfection of the secondary packaging. The packaging should comply with packing instruction P 650 and the European agreement concerning the international carriage of dangerous goods by road (ADR) - unless the requirements for transport by air apply, which may be higher. Samples should be labelled as biological substance, category B (UN3373).

Note: If FMDV has been cultured, it is mandatory to classify it as "Infectious Substances affecting animals, UN 2900" and pack it accordingly (packing instruction P 620). For air transportation, a "Shipper´s Declaration for Dangerous Goods" is necessary.

Laboratory biorisk management in FMD contingency laboratories

1. A biorisk officer (BRO) and deputy (DBRO) must be designated, and one or both present on-site at all periods in which samples are being received, and contactable at all periods when diagnostic activities are ongoing.
2. The BRO/DBRO must have sufficient experience and technical training to enable assessment of FMD risk and risk management procedures.
3. There must be a designated Restricted Zone with controls in place to limit human access.
4. Personnel must be authorised to enter the Restricted Zone by the BRO/DBRO.
5. Authorised personnel working in the Restricted Zone must be trained in biorisk management and evidence of the training recorded. Where facilities for the inactivation of waste from the Restricted Zone are located outside of this area, also staff working with such waste must be trained in biorisk management and evidence of the training recorded.
6. Authorised personnel must
   (a) change clothing before entering and after leaving the Restricted Zone ;
   (b) for at least 3 days after leaving the Restricted Zone not have any contact to animals of susceptible species, nor enter buildings or enclosed fields where animals of susceptible species are kept, and not handle items used in the care of susceptible species.

   The agreement of the authorised personnel to these conditions must be recorded and a reminder notice of these conditions placed in a visible location at the exit point of the Restricted Zone.
7. Entry and exit of personnel to the Restricted Zone should be recorded.
8. Entry and exit points to the Restricted Zone will be kept to the minimum– preferably a single point of entry/exit.
9. A step-over line, or other clearly demarcated boundary, shall indicate the exit point.
10. If possible, staff should shower out before leaving the laboratory premise. In case the shower facilities are not placed at the border of the Restricted Zone, outer protective garments, including shoes or shoes coverings, shall be removed before exit from the

Restricted Zone. All clothing worn in the Restricted Zone must be stored in a secure way, e.g. in designated lockers, until treatment.

11. An incident recording system, SOPs for risk identification and notification procedures and target response time, must be in place to ensure early notification of the authorities in the event that a risk of FMDV spreading from the lab has been identified.

12. The laboratory areas used for the receipt, testing and storage of suspect sample material must be designated and permit isolation from other essential activities in the laboratory. Once a positive sample has been identified, all potentially contaminated areas are classified as Restricted Zone. Access doors to this Restricted Zone should display a warning sign that access is restricted to authorised personnel only.

13. Changing facilities and lockers are required to enable staff to deposit unessential items outside the Restricted Zone.

14. Entering of the Restricted Zone by farmers or staff working on farms should be avoided. If possible, it should be attempted to separate vehicles bringing samples from vehicles entering the premise for other purposes.

15. Shower facilities must be available onsite, preferably at the border of the Restricted Zone.

16. Sample reception area

    (a) The Restricted Zone must contain a specified area for sample reception which must

    (b) be easily disinfected in the event that leakage of samples occurs into packing materials or following opening of the packages;

    (c) be equipped to enable repacking of samples into appropriate transport containers for dispatch to laboratories meeting the MBRM Standards for FMDV laboratories.

    (d) have suitable facilities for waste disposal and have hand-washing facilities at exit points.

17. Sample preparation area

    (a) The Restricted Zone must contain a specified area for serum separation and/or RNA extraction.

    (b) This area must have suitable facilities for surface disinfection and waste disposal and have hand-washing facilities at exit points.

    (c) Samples originating from a holding with clinical signs indicating the possible presence of FMD pose a higher risk. They must be opened and the subsequent liquid handling steps be carried out in a microbiological safety cabinet (MSC). Centrifugation should be carried out in closed rotors or sealed centrifuge buckets, which can contain a spillage in case the primary vessel fails.

    (d) Viral infectivity must be inactivated before further processing in all cases where this does not affect the intended diagnostic tests, e.g. by mixing with an appropriate buffer containing chaotropic salts prior to RNA extraction.

(e) Serum samples should be pre-treated by thermal inactivation for 2h at 56 ^{0}C in order to reduce infectivity titres as far as this is possible without impairing the intended serological testing regime or the validity of the tests used.

18. Testing area

(a) The Restricted Zone must contain a designated area for testing.

(b) This area must have suitable facilities for surface disinfection and waste disposal and have hand-washing facilities at exit points.

(c) The testing of serum samples originating from a holding with clinical signs indicating the possible presence of FMD by ELISA for antibody must be carried out in an MSC as far as possible.

(d) The testing of samples of vesicular material for antigen e.g. by ELISA or LFD poses the highest risk of all activities carried out in "FMD Contingency Laboratories". It must be carried out in a way that all liquid handling steps are performed in a MSC. If an incubator is used to guarantee the required incubation temperature, plates should be sealed or placed in a suitable secondary vessel.

(e) The testing of samples originating from a holding without clinical signs indicating the possible presence of FMD by ELISA for antibody should be carried out in a way that aerosol generation and spread is minimized. In particular, the initial steps including the first washing step are critical.

19. Sample storage area

(a) The Restricted Zone must contain a specified area for the storage of samples.

(b) This area must have suitable facilities for surface disinfection.

20. Communications and reporting office space

The laboratory must have an adequate provision of office space, computing and communications facilities (e.g. electronic communications, facsimile) to reduce the need to a minimum for staff, papers and physical records to exit the Restricted Zone.

21. Rest rooms

The Restricted Zone should have sufficient rest rooms and lavatory facilities in relation to the staff number expected at peak periods of activity, sufficient to reduce the need to a minimum for staff to exit the Restricted Zone.

22. Location of autoclave

Facilities for heat treatment with saturated steam must be present on the site, preferably with sufficient capacity for throughput at the maximum operating capacity of the laboratory.

23. Liquid waste

(a) Heat or chemical treatment of all waste water through a validated effluent treatment system is the preferred method, in compliance with requirements specified for FMD laboratories.

(b) Alternatively, or additionally, the laboratory may demonstrate that it has put in place a robust management system for inactivation liquid waste that is potentially contaminated with virus or has contacted risk materials. If treatment

of all liquid waste from the Restricted Zone (including waste water from the showers) is not possible, at least the ELISA buffers and washing fluids must be collected and treated.

24. Solid waste

(a) For biological, solid waste, and all solid disposable materials that have been in contact with potentially infectious specimens, treatment by wet-heat in an autoclave within or at an entrance point to the Restricted Zone is the preferred option.

(b) If such a treatment of all solid waste is not possible, it may be packaged into suitable hermetically sealed containers, surface decontaminated by a validated method at the exit from the Restricted Zone and removed for autoclaving outside of the Restricted Zone. Only if waste has been effectively chemically decontaminated prior to packaging may it be transported as clinical waste under ADR regulations (UN 3291).

26. Removal of equipment, materials and clothing from the Restricted Zone

(a) Removal of any material and equipment from the Restricted Zone shall be subject to authorisation by the BRO.

(b) The reason for removal, date and destination will be recorded.

(c) The BRO will ensure that materials and equipment which has been in contact with risk materials (specimens) will not be removed from the Restricted Zone without a validated treatment to inactivate FMDV.

27. Declassification of the Restricted Zone

(a) A decontamination plan must be agreed with the competent authorities, before restrictions can be lifted.

(b) If heat treatment or scanning of all paper from the Restricted Zone is not possible, it should be packed into suitable containers, which should be disinfected and kept under lock for at least two years. If the containers have to be opened before, this has to be done in a Restricted Zone meeting the standards described above.

(c) All clinical specimens handled in the Restricted Zone during a period when potentially infectious FMDV material was handled, should be considered as potentially contaminated with FMDV and should be destroyed before the declassification of the Restricted Zone. Alternatively the material needs to undergo a validated inactivation process and surface decontamination in order to be released. These samples and processes have to be approved by the BRO and/or the competent authority and documentation on these samples has to be maintained until the samples are destroyed by autoclaving, incineration, or a method approved for category 1 animal by-products (Regulation (EC) No 1069/2009 and Regulation (EC) 142/2011).