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FINAL REPORT OF A MISSION

CARRIED OUT IN

THE NETHERLANDS

FROM 08 TO 10 JUNE 2009

IN ORDER TO EVALUATE THE SECURITY SYSTEMS APPLIED IN ESTABLISHMENTS AND LABORATORIES HANDLING LIVE FOOT-AND-MOUTH DISEASE VIRUS

Executive Summary

The mission was carried out from 8 to 10 June. The mission team comprised two inspectors from the Food and Veterinary Office (FVO) and two experts from the Member States (MS), one in foot-and-mouth disease (FMD) and one for questions of bio-security in laboratories working with microbiological hazards.

The mission was undertaken as part of the FVO's planned mission programme and it was the first of a new series of FVO missions to evaluate the bio-security management systems applied at establishments and laboratories handling live FMD virus as listed in Annex XI of Council Directive 2003/85/EC.

The legal basis of the new series of missions is Article 66 of Council Directive 2003/85/EC which requires veterinary experts from the Commission to carry out spot-checks to ascertain whether the security systems applied in the establishments and laboratories handling live FMD virus comply with the bio-security standards set out in the "Minimum standards for laboratories working with foot-and-mouth virus in vitro and in vivo" established by the European Commission for the Control of Foot-and-Mouth Disease.

The FMD vaccine manufacturer "Lelystad Biologicals Ltd" (LB) is situated in the same facilities as the Central Veterinary Institute of Wageningen University and Research Centre (CVI-WUR). As they have a common bio-security management system both were inspected.

Article 65 of Council Directive 2003/85/EC has yet not been transposed into national legislation in respect of the control and the approval of establishments and laboratories handling live FMD virus by the CA and the application of the Minimum Standards (1993). Moreover, the change of the operator of the FMD vaccine manufacture unit has not been notified to the Commission services.

The mission team found that although there is a functioning audit system in place run by the CVI-WUR itself, the CA failed to meet the Community requirements in respect of its obligation to strictly control laboratories and establishments in which live FMD viruses are handled. Shortcomings were identified in respect of the approval of the facilities and of its operations and the responsibility for the inspection of both the LB and the CVI-WUR. While at LB and CVI-WUR the Minimum Standards (1993) have in general been met, not all aspects of the bio-security management system applied at LB and the CVI-WUR were considered best practice.

The report makes a number of recommendations to the CA, aimed at rectifying the shortcomings identified and enhancing the implementation and control measures in place.

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Abbreviations and definitions used in this report

Abbreviation	Explanation
BEI	Binary Ethylenimine
Bio-Risk	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) of such an exposure (as defined by the Minimum Standards (2009).
Bio-Safety	Containment principles, technologies and practices that are implemented to prevent the unidentified exposure to biological agents and toxins, or their accidental release (as defined by the Minimum Standards (2009).
Bio-Security	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 (as defined by the Minimum Standards (2009).
CA	Competent Authority
CVI-WUR	Central Veterinary Institute of Wageningen University and Research Centre
EU	European Union
FAO	Food and Agriculture Organisation
FMD	Foot-and-Mouth Disease
FVO	Food and Veterinary Office
GMP	Good Manufacturing Practice
HCU	High Containment Unit
HEPA filter	High Efficiency Particulate Air filter
Lab	Laboratory

LB	Lelystad Biologicals Ltd
Minimum Standards (1993)	"Minimum Standards for laboratories working with foot-and-mouth virus in vitro and in vivo" established by the European Commission for the Control of Foot-and-Mouth Disease of the Food and Agriculture Organisation, 26th session, Rome, April 1985, as modified 1993
Minimum Standards (2009)	"Minimum Standards for laboratories working with foot-and-mouth virus in vitro and in vivo" established by the European Commission for the Control of Foot-and-Mouth Disease of the Food and Agriculture Organisation, 38th session, Rome, April 2009.
Ministry of LNV	Ministry of Agriculture, Nature and food Quality
MS	Member State
SOP	Standard Operational Procedure
VWA	Food and Consumer Goods Safety Authority

1 Introduction

The mission took place in the Netherlands from 8 to 10 June 2009. The mission was undertaken as part of the FVO's planned mission programme. It was one of a series of mission in the MS handling live FMD virus.

The mission team comprised two inspectors from the FVO and two experts from the MS, one in FMD and one for questions of bio-security in laboratories working with microbiological hazards.

2 Objectives Of The Mission

The objective of this series of missions was to evaluate whether laboratories and establishments handling live FMD virus in the European Union (EU) meet or exceed the minimum requirements laid down in the "Minimum standards for laboratories working with foot-and-mouth virus in vitro and in vivo" established by the European Commission for the Control of Foot-and-Mouth Disease of the Food and Agriculture Organisation (FAO), 26th session, Rome, April 1985, as modified 1993 (hereafter, Minimum Standards (1993)), referred to Annex XII to Council Directive 2003/85/EC.

3 Legal Basis for the Mission

The legal basis of the series of missions is Article 66 of Council Directive 2003/85/EC which requires veterinary experts from the Commission to carry out spot-checks to ascertain whether the security systems applied in the establishments and laboratories handling live FMD virus comply with the bio-security standards set out in the "Minimum standards for laboratories working with foot-and-mouth virus in vitro and in vivo" established by the European Commission for the Control of Foot-and-Mouth Disease.

4 Background

Article 66 of Council Directive 2003/85/EC provides that veterinary experts from the Commission, in collaboration with the CA of the MS, shall carry out spot-checks to ascertain whether the security systems applied in the establishments and laboratories handling live FMD virus comply with the bio-security standards set out in its Annex XII. The latter are the Minimum Standards (1993). In April 2009, new standards were adopted by the European Commission for the Control of FMD of the FAO, 38th session in Rome (Minimum Standards (2009)). As Council Directive 2003/85/EC did not refer to these new standards at the time of the mission was carried out, the bio-security system inspected during the mission was checked against the Minimum Standards (1993).

Part A of Annex XI to Council Directive 2003/85/EC lists the laboratories and establishments authorised to handle live FMD virus including the "Central Institute of Wageningen UR, Lelystad" (CVI-WUR). Part B lists laboratories authorised for the production of FMD vaccine including the "CIDC-Lelystad, Central Institute for Animal Disease Control, Lelystad".

During the opening meeting the mission team was informed by the CA that the actual FMD vaccine manufacturer is not longer the "CIDC-Lelystad, Central Institute for Animal Disease Control, Lelystad" but "Lelystad Biologicals Ltd" (LB) using the facilities of the "CIDC-Lelystad, Central Institute for Animal Disease Control, Lelystad". LB and CVI-WUR are situated in the same

facilities. The CA requested to include both LB and the CVI-WUR in the inspection because they have a common bio-security management system. The mission team agreed to this proposal.

5 Findings And Conclusions

5.1 Competent Authorities

5.1.1 Legal requirements

Article 65 of Council Directive 2003/85/EC requires the Member States to ensure that

(a) laboratories and establishments in which live foot-and-mouth disease virus, its genome, antigens or vaccines produced from such antigens are handled for research, diagnosis or manufacture are strictly controlled by the competent authorities;

(b) the handling of live foot-and-mouth disease virus for research and diagnosis is carried out only in approved laboratories listed in Part A of Annex XI;

(c) the handling of live foot-and-mouth disease virus for the manufacturing of either inactivated antigens for the production of vaccines or vaccines and research is carried out only in the approved establishment and laboratories listed in Part B of the Annex XI.

5.1.2 Findings

5.1.2.1 Transposition of Council Directive 2003/85/EC

Council Directive 2003/85/EC was transposed into Dutch legislation according to a table in Annex 2 of the FMD contingency plan of the Netherlands. This table was the basis of the official notification to the Commission services of implementation by the CA.

However, the mission team noted that

- Article 65 of Council Directive 2003/85/EC, which requires the control and the approval of establishments and laboratories handling live FMD virus by the CA and the application of the Minimum Standards (1993), has not been transposed into national legislation.

5.1.2.2 Designation of the competent authority

In accordance with the information provided by the CA, within the Ministry for Agriculture, Nature and Food Quality (LNV) the Directorate for Food and Veterinary Affairs is the CA for the approval of LB and of the CVI-WUR.

5.1.2.3 Approval of the CVI-WUR and LB to handle live FMD virus

According to the information provided by the CA, several decades ago the “State Veterinary Research Institute”, which at the time was situated in Amsterdam and in the early 1970s of last century moved to Lelystad under the name Central Veterinary Institute, was approved by the Dutch government to handle live FMD virus. No other laboratories in the Netherlands are allowed to work

with FMD virus.

The mission team noted that

- since the first general approval granted several decades ago, the approval was never renewed to reflect the major changes to the construction of the facilities, new operators and new activities. There is however, no doubt that all changes concerning this Veterinary Institute in Lelystad were carried out in consensus with the Dutch government.
- no official approval has been granted to LB for the authorisation to handle live FMD virus for the production of FMD vaccine as required by Article 65 (c) of Council Directive 2003/85/EC.
- the change of the operator of the FMD vaccine manufacture unit has not been notified to the Commission services in order to up-date the list of establishments and laboratories authorised to handle live FMD virus for the production of FMD vaccine set out in Part B of Annex XI to Council Directive 2003/85/EC.

5.1.2.4 Operations and structure of the CVI-WUR and LB

The CVI-WUR is a private body and it is part of the "Animal Sciences Group" of the University of Wageningen which has the overall responsibility for the CVI-WUR.

The CVI-WUR has a secured and fully isolated laboratory including a High Containment Unit (HCU). On the site of the CVI-WUR, LB produces FMD vaccines at present mainly for emergencies within the Netherlands. LB is integrated in the facilities of the CVI-WUR and shares, in particular, the bio-risk management system of the HCU of the CVI-WUR.

The mission team noted that

- LB has to meet the requirements for bio-security management system set out and implemented by the CVI-WUR;
- the Ministry of LNV is responsible for possible consequential losses originating from the use of the HCU of the CVI-WUR and guarantees up to € 2.6 million per year for bio-security operations of the CVI-WUR in order to ensure that this system is fully operational throughout the year, without depending on income gained by services to third parties. The CVI-WUR is allowed to provide a restricted laboratory service to private business and rents out part of its facilities to LB.

The Management Director of the CVI-WUR together with both the Bio-Safety Executive and the Management Executive bears the responsibility for the bio-security management operations of the CVI-WUR. They are supported by the Bio-Safety Committee and in case of emergencies by the Bio-Safety Crisis Unit. The Bio-Safety Committee holds 10 meetings a year where aspects of bio-security management at the CVI are discussed.

There is a reporting system in place based on the minutes of the Bio-Safety Committee and its annual reports to the LNV. A decision-tree defines precisely in which cases of emergencies the Ministry of LNV has to be informed.

As FMD bio-risk management is a highly specialised field with only a limited number of experts available, the bio-security management measures have been developed over several years and implemented by the CVI-WUR. They have been discussed and approved by the CA. Staff members of the CA are agenda members of the Bio-Safety Committee of the CVI-WUR and scrutinize the reports. If considered necessary, follow up discussions and actions were initiated.

In 2006, the CVO handed over the responsibility for issuing import licenses of biological materials

to the Food and Consumer Goods Safety Authority (VWA) within the Ministry of LNV.

The mission team noted that

- the VWA issued general permissions to import biological materials, without specifying the biological materials which can be imported to various facilities of the "Animal Sciences Group" not taking into account that only the CVI-WUR is entitled to receive material containing FMD virus.

5.1.2.5 Inspection of the CVI-WUR and LB

Regarding inspection of the facilities of CVI-WUR and the LB, the CA relies on the self-auditing system applied by the CVI-WUR and the reports received thereof.

The mission team noted that

- the CA considers that the bio-security management system in place is able to verify compliance with the Minimum Standards (1993) and the obligations of the CA as required by Article 65 of Directive 2003/85/EC.
- the Ministry of LNV did not carry out any inspection on the bio-security management system at the CVI-WUR and LB within the last two years;
- the Ministry of LNV did not formally hand over its inspection responsibility for the CVI-WUR and the LB to the CVI-WUR;
- the Bio-Safety Executive and his staff oversee the bio-security management situation of the CVI-WUR.
- in the annual reports the Bio-Safety Committee has stressed repeatedly the necessity for independent audits of the CVI-WUR. As the CVI-WUR recognised the advantage of external, independent audits, it organised such audits in 1999 with a Dutch / Belgian team and in 2005 with a Belgian / Swedish team.
- in 2007 the Ministry of LNV arranged for a "risk assessment' inspection in respect of the proposed privatisation of the vaccine production unit within the CVI-WUR which included a review of the bio-security management system.
- at present, the responsibility for the inspections of the bio-security system of LB and the CVI-WUR is not defined and clearly allocated. On one hand the Directorate for Food and Veterinary Affairs of the Ministry of LNV does not carry out on spot-checks and relies on the self-auditing system of the CVI-WUR, and on the other hand the municipality of Lelystad carries some responsibility in view of the fact that in the Netherlands permits to build a laboratory have to be issued by the municipality. The municipalities rely on the Ministry of Environmental Affairs for support, including bio-security aspects during their on spot-checks at the CVI-WUR and at LB.

5.1.2.6 Qualification of the CA inspectors

The only official controls of both the LB and the CVI-WUR are at present carried out by inspectors of the municipality of Lelystad.

The mission team noted that

- following the information provided by the Bio-Safety Team of the CVI-WUR, which supports the Bio-Safety Executive, the professional background of the inspectors of the local (municipal) authorities does not necessarily include experience in the field of bio-security management to evaluate adequately the complex and highly sophisticated system applied at

LB and at the CVI-WUR.

5.1.3 Conclusions

Council Directive 2003/85/EC has not been transposed into national legislation in respect of the control and the approval of establishments and laboratories handling live FMD virus by the CA and the application of the Minimum Standards (1993).

Shortcomings were identified in respect of the approval of the facilities and of its operations, the responsibility for the inspection and the granting of import permissions of biological material including FMD virus into non-approved establishments or laboratories.

Although there is no doubt that there is a functioning audit system in place run by the CVI-WUR itself, there is currently no national legal framework for inspection of both LB and the CVI-WUR. From that point of view the CA failed to meet the Community requirements in respect of its obligation to strictly control laboratories and establishments in which live FMD viruses are handled for research, diagnosis or vaccine production.

5.2 BIO-SECURITY STANDARDS

Legal requirements

Article 65 (d) of Council Directive 2003/85/EC requires that laboratories and establishments handling live FMD virus must meet or exceed the minimum bio-security standards laid down in the Minimum Standards (1993).

The numbering of the legal requirements used in this report follows the numbering used in the Minimum Standards (1993).

The mission team used for the inspection of LB and the CVI-WUR a 37-page check-list which reflects the provisions of the Minimum Standards (1993).

5.2.1 Personnel

5.2.1.1 Legal requirements

The Minimum Standards (1993) sets out requirements for (1) the prevention of illegal entry to the restricted area, (2) the training of staff, (3) the conditions for the entry into and exit from the restricted area, (4) a code of disease security practice, (5) emergency evacuation procedures, (6) avoiding contact with FMD susceptible animals at home and (7) appropriate laboratory clothing.

5.2.1.2 Findings

The mission team noted that

- the restricted areas are only accessible through locked doors of sound construction. Staff are only admitted to the restricted areas following a bio-security induction, which is carried out in several stages to accommodate the different needs from supervised visitors to

independently working staff, working in different areas.

- all staff are obliged to familiarise themselves with the code of practice for bio-safety/bio-security, which is regularly updated and provides a good overview for all processes and directs the users to the more detailed standard operational procedures (SOPs). Adequate quarantine restrictions are in place.
- laboratory (lab) personnel do not wear lab coats, but wear additional lab coats in the canteen.
- retraining of staff only occurs through the issuing of new/revised SOPs through a modern electronic document control system. There is no system for regular retraining of experienced staff.

5.2.1.3 Conclusions

The bio-security management system in respect of the requirements for the personnel is, in general, well developed. However, the retraining of experienced staff entering the high containment area infrequently is considered insufficient.The clothing of the lab personnel is not considered best practice.

5.2.2 Buildings

5.2.2.1 Legal requirements

The Minimum Standards (1993) sets out requirements for (8) the general construction of buildings and their surfaces, including ducting of the air conditioning system, (9) windows, (10) doors, (11) walls, floors and ceilings.

5.2.2.2 Findings

The mission team noted that

- the buildings date back to the early 1970s and most parts have undergone more than one refurbishment cycle. One area at the interface of building 242 and 241 is currently externalised and undergoing refurbishment to improve the ventilation and air filtration. A temporary wall of marine ply was erected for the purpose of containment. The temporary barrier was tested prior to externalising the area.
- the building is split into a number of discrete independently-operated restricted areas. The vaccine manufacturing side under control of LB is all located in the ground floor of building 251 and is divided into a cell and media production area, the virus production area and the downstream processing area. All of these areas operate under Good Manufacturing Practice (GMP), but in addition the latter two areas are also FMD virus containment zones with their own shower barriers. Due to quarantine restrictions the inspection team could only visit the cell production and virus production, but not the down stream processing area.
- the topography of the different zones necessitates pumping virus antigen across the cell production area from virus production to down stream processing. The basement below the virus production area is not part of the containment area, but access to it is restricted (khaki area). The drains from the virus production and downstream processing pass through the basement into the restricted area under the diagnostic laboratory wing.
- areas that do not meet current standards have been excluded from the containment area and isolated as khaki areas, e.g. the floor above the virus production area and disused parts of the

animal facilities.

5.2.2.3 Conclusions

While the buildings date back some decades they are generally well maintained. The system of khaki areas is an effective control to restrict access and maintain a protocol for areas that are on or adjacent to the containment barrier.

5.2.3 Air

5.2.3.1 Legal requirements

The Minimum Standards (1993) sets out requirements for (12) air removal, (13) the use of HEPA filters for exhaust air, (14) the filter installations, (15) the use and installation of manometers measuring the negative pressure, (16) the laboratory power supply, (17) vertical flow safety cabinets, (18) the monitoring of the ventilation system, (19) efficiency tests of filters before installation, (20) efficiency tests of filters following installation or replacement, (21) the methods for testing the efficiency of filtration, (22) conditions for changing the filters and (23) conditions for testing and changing of the filters in safety cabinets.

5.2.3.2 Findings

The mission team noted that

- area pressures are only transmitted to the building management system, so that users cannot verify that the area they are entering or working in is operating at the correct pressure. It also places a high reliance on the technical team to promptly communicate ventilation failures to the users. That is not easy in animal rooms as they can only be reached via the telephone and the technical staff have to know where and if staff is working in an area.
- the air supplies on the animal rooms are protected by a damper from reverse air flow during a ventilation failure. There is only a single bag filter (45%) in the supply air path to each room. During inspection insects were roosting in the filter box of the bag filter in one unused animal room. The installation of the bag filter does not lend itself to reliable protection against insect ingress into the animal rooms. As insects such as Culicoides can exit rooms with the operators to the outside this should be considered as a possible escape route for insect vectors, particularly where the access lobby is entered from the open air.
- the supply air damper shuts as required but is not airtight and located on the intake side of the air handler. Because it is not directly at the containment barrier and the ductwork and supply air handler boxes are not air tight, the room containment relies heavily on the inward airflow, which is achieved by a single exhaust air handler and a secondary safeguard in the form of duct from the animal room to the central corridor with a High Efficiency Particular Air (HEPA) filter on the central corridor side. The central corridor is on a separate air handling system. As a setup this arrangement provides a level of resilience that provides containment while the room and/or central corridor ventilation plants are working, but only limited static containment during ventilation failures.
- the exhaust HEPA filters in a number of areas are close coupled and can only be tested as

one unit. The inability to test the filters individually removes the integrity from the secondary HEPA filter as an independent control. The test criteria applied to the sandwich are not higher than the criteria for an individual filter. This also applies to the exhaust HEPA filters serving the area occupied by LB. The test points for injecting and sampling the aerosol challenge appear to be positioned too close to the filters. Upstream there is not enough distance for dispersion of the test aerosol across the filter face and downstream the distance is not sufficient for the laminar air flow coming out of the HEPA to disperse so that sampling is representative of the full filter face. Unless there are distribution pipes fitted upstream on the filters and dispersion panels down stream, this setup is not considered to provide valid test results for the overall filter performance. Some reassurance is provided by the fact that all filters are tested pre-installation on site and the seal, which is considered the most critical leak path on a certified filter, is tested independently on each filter panel using the DIN seal channel. Due to time constraints during the inspection no clarification was received about the question whether for regular re-testing the performance of the bulk test is evaluated to ensure that the test points are in positions that allow a valid test.

5.2.3.3 Conclusions

While the requirements set out in the Minimum Standards (1993) have been in general met, not all aspects of the bio-security management system applied at LB and the CVI-WUR in respect of air treatment were considered best practice, in particular in respect of

- the installation of local pressure indicators and alarms in strategic points;
- the ventilation system of the animal facilities. Supply HEPA filter protection is considered standard in animal rooms;
- vector control in relation to flying insects;
- close-coupled double HEPA filters, which can only be tested as one unit. The inability to test the filters individually removes the integrity from the secondary HEPA filter as an independent control.

5.2.4 Effluent

5.2.4.1 Legal requirements

The Minimum Standards (1993) set out requirements for (24) the treatment of effluent, including liquids (26 – 29) and solid waste (30 – 32) and (25 and 33) the monitoring system for the treatment of the effluent.

5.2.4.2 Findings

The mission team noted that

- effluent from all zones is carried via gravity drains through the basement to a common effluent treatment area, which consists of 2 storage tanks and two continuous flow effluent treatment plants which operate in duty / standby. Only under the vaccine production area the drains are located outside the actual containment barrier, which is not ideal. In recognition of this situation the critical drain runs from this area that would potentially carry virus

production effluent charged with high titre virus have been changed to stainless steel. There is no basement under the ground floor areas that house the large production vessels. Effluent pipes from this area pass through the slab and are not inspectable from the outside for 1-2 metres in the slab.

- as a secondary control leak detectors are installed on the floor in each area of the basement. In two different areas floor leak detectors were manually activated. The response to an activation of the leak detector was very impressive. Within 4 minutes two engineers in the correct clothing attended to the alarm, which was logged on the software of the bio-risk management system. With this rapid staff response time the risk is managed very effectively.
- drains connecting the clean areas to the effluent drainage system of the containment are isolated by deep seal traps. A protocol is in place to regularly top up these traps in areas of little use. This is regarded as a satisfactory management control.
- drain vents have been reduced to a minimum. Adjacent to the effluent treatment zone under the animal facility the drain vents open into the basement space. This space is in containment, but the open venting does not fit the principles of containing the hazard as close to source as possible. The basements are not easy to clean as the surfaces are unpainted and not impervious to water. In the laboratories all virus containing liquids are handled in microbiological safety cabinets, but in the effluent treatment zone the pipe systems are open. There is no explicit requirement in the minimum standards for primary containment of effluent but the current arrangement turns the basement essentially into primary containment, where different floor surfaces would be expected.

5.2.4.3 Conclusions

The continuous flow system is well designed and appears to operate satisfactorily. The treatment parameters (30 minutes at ≥ 121 degree C) exceed the minimum requirements comfortably.

While the requirements set out in the Minimum Standards (1993) have in general been met, not all aspects of the bio-security management system applied at LB and the CVI-WUR in respect of effluent treatment were considered bet practice, in particular not in respect of

- the primary containment of the effluent pipes in order to contain contaminated material better at source and reduce the likelihood of operator exposure.

5.2.5 Equipment and materials

5.2.5.1 Legal requirements

The Minimum Standards (1993) set out requirements for (34 – 36) laboratory fittings, (37 – 39) the handling of FMD virus and (40 – 48) the removal of equipment and material.

5.2.5.2 Findings

The mission team noted that

- a twin rendering plant is used for decontamination of animal carcasses. This is located outside the containment envelope in a dedicated room that is accessed only in khaki clothing

and the extracted air from the room is HEPA filtered.

- three routes are used for externalising equipment: steam autoclaves, ethylene oxide sterilizers, and formaldehyde fumigation chambers. The processes are delegated to other teams and not directly under the supervision of the bio-safety team.
- virus production solids are separated from the liquid phase using a paper filter with diatomaceous sand as a filter aid. After the run the filter bed is treated with hydrochloric acid and filters are discarded by opening the primary containment. No information was provided on the validation of the inactivation process. During the filter change the waste materials from the filter regularly spill on the floor. The integrity of the filter is important to prevent cell debris / solids from leaking into the product prior to binary ethylenimine (BEI) treatment. The method to decontaminate the filter allows the primary containment to be opened after the filter is inactivated by a validated means. Means of monitoring the movement of the agitator in the BEI inactivation vessel are not available.
- during the inspection there was insufficient time to conduct a comprehensive survey of all equipment that is used in the laboratory and evaluate the level of primary containment effected. The safety staff were fully aware of the issues relating to aerosol containment from equipment such as centrifuges, sonicators, flow sorters and freeze driers.
- one centrifuge was discussed with staff in the LB quality control lab. Staff use this centrifuge for low speed centrifugation of virus-containing liquids. The tubes in the centrifuge are sealed and the centrifuge lid has a rubber seal, but the rotor and buckets were not sealed. In the event of a spill, aerosol would be released directly to the laboratory. Tubes and tube seals fail from time to time, so that it is considered good practice to provide a secondary seal at the level of the swing out buckets or centrifuge rotors.
- the management of transferring biological materials from the restricted area is left to the scientist moving the material and the technical staff member operating the dunk tank. This is not considered an adequate control for movement of biological materials that are destined to leave the site. There is no independent oversight/peer review of this process by a person with the biological knowledge and experience in order to ensure that the risk of releasing FMD virus to low containment labs is effectively managed.

5.2.5.3 Conclusions

While the requirements set out in the Minimum Standards (1993) have in general been met, not all aspects of the bio-security management system applied at LB and the CVI-WUR in respect of the treatment of equipment and material were considered best practice in particular not in respect of

- the validation of the filter integrity of the cell separation filter before and after use so as to exclude the possibility of introducing solids into the liquid batch for BEI inactivation;
- the method to decontaminate the filter, so as to ensure that the primary containment is opened only after the filter is inactivated by a validated means;
- the means of monitoring the movement of the agitator in the BEI inactivation vessel as this can be a cause of failed inactivation;
- the management of transferring biological materials from the restricted area;
- the restriction of the centrifugation of infectious materials to centrifuges which prevent aerosol release to the laboratory (sealed rotor or centrifuge bucket).

6 Overall Conclusions

Council Directive 2003/85/EC has not been transposed into national legislation in respect of the control and approval of establishments and laboratories handling live FMD virus and the application of the Minimum Standards (1993).

Although there is no doubt that there is a functioning audit system in place run by the CVI-WUR itself, the CA failed to meet the Community requirements in respect of its obligation to strictly control laboratories and establishments in which live FMD viruses are handled for research, diagnosis or vaccine production. Shortcomings were also identified in respect of the approval of the facilities and of its operations and the responsibility for the inspection of both the LB and the CVI-WUR.

While at LB and the CVI-WUR the Minimum Standards (1993) has in general been met, not all the aspects of the bio-security management system applied at LB and the CVI-WUR were considered best practice.

7 Closing Meeting

A closing meeting was held on 10 June 2009 in Lelystad with representatives of the CA and of the CDI-WUR and LB. At this meeting, the main findings and conclusions of the mission were presented by the inspection team. The CA stated that corrective actions would be start immediately.

8 Recommendations

The competent authorities are invited to provide, within one month of receipt of the report, an action plan containing details of the actions taken and planned, including deadlines for their completion, to address the following recommendations:

N°.	**Recommendation**
1.	To transpose Article 65 of Council Directive 2003/85/EC into national legislation in respect of the control and the approval of establishments and laboratories handling live FMD virus by the CA and the application of the Minimum Standards (1993).
2.	To ensure that the Commission services are informed about the changes in respect of the entries in the lists of establishments and laboratories authorised to handle live FMD virus in order to up-date these list set out in Annex XI to Council Directive 2003/85/EC.
3.	To ensure that the establishments and laboratories handling live FMD virus are approved as required by Article 65 (b) and (c) of Council Directive 2003/85/EC.
4.	To ensure that the CVI and BL is strictly controlled by the CA as required by Article 65 (a) of Council Directive 2003/85/EC.

N°.	Recommendation
5.	To ensure that permits to import material containing FMD virus are only issued to establishments and laboratories approved for that purpose, as required by Article 65 (b) and (c) of Council Directive 2003/85/EC.
6.	To consider improving the aspects of the bio-security management system applied at LB and the CVI-WUR which are described in the conclusions of Chapter □5.2 Bio-security Standards□ of this report.

Annex 1 - Legal References

Legal Reference	Official Journal	Title
Dir. 2003/85/EC	OJ L 306, 22.11.2003, p. 1-87	Council Directive 2003/85/EC of 29 September 2003 on Community measures for the control of foot-and-mouth disease repealing Directive 85/511/EEC and Decisions 89/531/EEC and 91/665/EEC and amending Directive 92/46/EEC