Risk assessment of the foot-and-mouth disease (FMD) antigen production plant (APP), Houtribweg, Lelystad, The Netherlands

A study commissioned by the Dutch Ministry of Agriculture (LNV)

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Executive summary

1. In order to make a comparison of the risks associated with a change in the use of the antigen production plant (APP) it was first necessary to define a base-line comparator. This was taken as the situation that existed during 2004/2005/early 2006 when the APP was being used to produce FMD antigen for both the Ministry and Intervet. The greatest hazard associated with the APP was when animals were infected with FMD virus.

2. The hazard associated with the activities of CIDC-Lelystad during 2004/2005/early 2006 was considerably greater than that associated with the APP since CIDC-Lelystad infected more animals with FMD virus. Mostly cattle were involved but some experiments involved pigs. On average two experiments involving the exposure of pigs to FMD virus were carried out in recent years by CIDC-Lelystad whereas for the APP only one experiment was done, in 2006, with pigs.

3. It is not possible to predict how many animals might be exposed to FMD virus by CIDC-Lelystad and the APP in the future. However, it can be speculated that if the FMD vaccine production activities at APP were to stop altogether it is theoretically possible that greater use would be made of the animal isolation facilities in the HCU by CIDC-Lelystad (and/or Third Parties) and in that case the level of hazard would increase, especially if pigs were involved. However, the biosecure systems are designed to manage such hazards and so the overall risk for the site should not increase.

4. The continued use of the APP for the production of FMD vaccine (or other highly contagious viruses/microbes) with current personnel, operating under the same biosecurity and GMP standards as was the situation during 2004/2005/early 2006, would be the most desirable future scenario for the APP since the level of hazard would not be significantly changed from that which existed previously. In the case of increased APP and animal experiment activities (evolved from an ambitious new owner) this will increase the challenge to the biosecurity systems. However, as stated in 3 (above), these where designed and are operated for this purpose and have proven to be fully effective.

5. Although it would be technically feasible to use the APP for the production of non-FMD vaccines or other products, the current GMP license (the part for the Houtribweg location) is for FMD antigens only and so a change to another agent would not be covered and there would be a need to make a fresh application. The re-establishment of GMP accreditation for the changed operating procedures would probably be a lengthy process but should not delay the selling process since pending qualification the new

GMP requirements could be introduced through intensive training (external and on the job) under the supervision of experienced staff.

6. The Commission has recommended a series of conditions for inclusion in the contract with the new owner to ensure that the company complies unconditionally with the biosecurity and GMP requirements and thereby maintains the relatively low risk profile of the APP. A requirement of GMP is that personnel must be qualified and experienced. This gives a safeguard against the possible employment by a new owner of unsuitable personnel.

7. The biosecurity officer of CIDC will have a key role to play in ensuring that the new owner and his/her employees comply with the security regulations issued by CIDC-Lelystad.

8. The Commission has recommended a series of measures to ensure that the APP can be operated under new ownership without interference with the statutory or reference activities of CIDC-Lelystad.

9. The APP could present a potential target for bioterrorists through breakage and entry or infiltration. However, the Commission concluded that the risk is relatively low as there are softer and less complicated targets elsewhere.

10. The situation at the Institute for Animal Health (IAH), Pirbright, UK has many similarities to that which could evolve at CIDC-Lelystad. At Pirbright the IAH has rented some of its buildings and facilities to a series of vaccine production companies over a 46 year period. This has resulted in the generation of a significant income stream for IAH, improved the opportunities for scientific exchanges between the two establishments and increased the availability of reagents for research purposes and a ready stockpile of vaccine during national FMD emergencies. The statutory and reference activities of IAH have not been compromised by the association and any disadvantages have been few in number and only of a minor nature.

Dates of Mission: 7 to 9 February 2007

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1. Background

The foot-and-mouth disease (FMD) Antigen Production Plant (APP), located in the High Containment Unit of the Central Institute for Animal Disease Control (CIDC)-Lelystad, belongs to ID-Lelystad Inc. FMD antigen is produced at the HCU-facilities of CIDC-Lelystad but vaccine formulation and filling is done at the ID-Lelystad Inc. facilities at Edelhertweg about 5 km away. CIDC-Lelystad and ID-Lelystad both belong to Wageningen University and Research Centre (Wageningen UR) but are different legal bodies. Until 2006 the APP had two contracts to produce foot-and-mouth disease antigen: (i) a contract with Intervet to produce FMD antigen and vaccine for commercial exploitation; and (ii) a contract with the Dutch Ministry of Agriculture to produce antigen for the Dutch emergency FMD vaccine bank. The contract with Intervet was terminated on 31 March 2006. The contract with the Ministry of Agriculture will continue until 1 January 2008 but after that date the Ministry will purchase vaccines for the emergency vaccine bank on the international market and not preferentially from the APP as was the previous arrangement.

The Dutch Ministry of Agriculture has convened a Commission to advise on whether Wageningen UR should sell the APP to a commercial vaccine or other company, and if so, what conditions should be imposed to ensure that there is no increase in the biosecurity risk. "Sell" in this context means giving access to the technical and scientific knowledge for the operation of the APP facility in compliance with good manufacturing practice (GMP) and the procedures for producing safe and efficacious FMD antigen and vaccine. Included would be the FMD antigen production equipment in the APP of ID-Lelystad at the HCU of CIDC-Lelystad, Houtribweg and the vaccine formulation and bottling equipment at ID-Lelystad, Edelhertweg. Also, trained and experienced staff and permits

(including GMP) are involved. The APP building and essential installations/utilities cannot be sold because they form an integral part of the HCU which belongs to CIDC-Lelystad of Wageningen UR. (Additional items for sale are: the technical and scientific knowledge for the production of tuberculin; equipment for producing tuberculin and existing contracts but these are not part of the present assessment. It is the intention that both activities will be sold as on entity).

The Ministry of Agriculture has commissioned to CIDC-Lelystad statutory tasks related to the surveillance and control of infectious animal diseases and operates to this purpose a HCU under a strict biosafety regimen (BSL3/4). To avoid interference with interests of other stakeholders CIDC-Lelystad has also to obey the Statute for Statutory Tasks (SST), which means that it is not allowed to accept research contracts from private parties. ID-Lelystad Inc. is committed to other research contracts from the government and private parties. The HCU is used by CIDC-Lelystad for research and diagnostic purposes (statutory tasks) and by ID-Lelystad for research, FMD antigen production and animal experiments.

2. Terms of reference

The Commission was asked to comment and advise on the following key questions.

2.1 What are the (safety) risks of selling the FMD antigen production plant* in Lelystad?

2.2 What problems can we expect in relation to the interference between production activities of a new owner and the reference (statutory) tasks of CIDC?

2.3 Under which conditions is a decision to sell acceptable from a risk management point of view?

2.4 For all the questions the focus of the committee shall be on the biosecurity risks, statutory aspects and necessary restrictions.

The complete list of key questions and sub-questions/elements to be considered is attached as Appendix 1.

** The Terms of Reference state "FMD vaccine production plant" but since only FMD antigen is produced in the HCU at Houtribweg, and this facility is the subject of the assessment, the Commission has used the phrase "FMD antigen production plant (APP)", instead.*

3. Description, management and operation of the FMD antigen production plant

The APP is an integral part of the CIDC high containment unit (HCU) (Appendix 2) but it has separate heating, ventilation and air condition (HIVAC) systems. The APP has its own heat exchangers fed by a central steam boiler. The liquid waste from the APP is pre-treated with a commercial disinfectant before discharge. After antigen production the waste will also contain BEI from the virus inactivation procedure (residual BEI will first have been neutralized in the inactivation vessel by the addition of excess thiosulphate). Each of the three separate units in the APP (see later) has a dedicated liquid waste storage tank and from these the waste is pumped to a central tank before final discharge in a sealed pipe, to CIDC's effluent treatment plant where batches of effluent are heated in the ALINO (steriliser). The ALINO is a continuous system where liquid waste is treated at 121^0 C for a minimum of 21 minutes. The construction of the tanks and pumps will prevent flow-back. Liquid waste from outside the closed systems (small volumes of cleaning water) are not pretreated before transport to the ALINO. Steam is delivered from CIDC's central boiler unit to the APP. The inlet air vents to the APP are protected by single HEPA filters (two for the virus rooms), the outlet vents by two HEPA filters in series. In the event of a power failure a diesel generator provides power to all the key electrical installations, including the HCU. The cut-in time is around 5 to 6 seconds and, on average, emergency power generation is required about once per year. The emergency power generator is tested once per week for one hour.

The Director of CIDC is responsible ensuring that all of the biosecurity systems and operational activities at CIDC-Lelystad, in particular those associated with the HCU, are maintained and operated properly. He is also responsible for ensuring that all staff on site and visitors comply with the biosecurity rules as detailed in the CIDC Biosecurity Manual (HCU veiligheidsvoorschrift versie 2004). Day-to-day responsibility is delegated by the Director to the Biosecurity Officer (BSO). The Director reports to the Chief Veterinary Officer (CVO). In the event of a biosecurity incident, if the BSO is not satisfied with remedial actions taken by the Director, he has the right to approach a higher authority in the Ministry.

CIDC is permitted to manipulate all 7 serotypes of FMD virus under a permit. In 2006 the permit was issued by the Dutch Food Safety Authority whereas formerly the permit was issued by the CVO. ID-Lelystad, in turn, permits the APP to produce and sell FMD antigen under a "manufacturing and distribution permit" issued by the Veterinary Medicinal Products Unit of the CBG-MEB. The APP is GMP-accredited and a GMP inspection is scheduled for late 2007. The services provided to the APP by CIDC are covered by service level agreements (SLA's). A chart showing the bodies with legal responsibility for the operation of the APP is given in Appendix 3. It should be underlined that although CIDC-Lelystad is part of the organisational structure of Wageningen UR it was separated from

ID-Lelystad a few years ago in order to avoid any accusations of a conflict of interest between the statutory work done for the Ministry (including the evaluation of commercial veterinary medicinal products) and contract research for private parties (e.g. vaccine industry).

The APP is comprised of three separate but adjacent operational units: (i) a Cell Culture Unit; (ii) a Virus Culture Unit; and (iii) a Downstream Processing Unit. The air pressure in the Cell Culture Unit is positive compared to atmosphere while that in the other two units is negative. BHK-21 cells for antigen production are grown in the Cell Production Unit (CPU). FMD virus is not manipulated in this area. When a sufficiently large quantity of BHK-21 suspension cells has been produced it is piped from the CPU to a large (2,000 litre) vessel in the Virus Culture Unit (VCU). An inoculum containing the selected strain of FMD virus is transferred into the 2,000 litre vessel containing BHK-cells and the growth of virus proceeds. The procedure involving the connection of the pipe from the inoculum container to the virus culture vessel is the only occasion when a piece of equipment containing infectious virus is opened (the inoculum container is handled/opened in a Biohazard LAF cabinet). All other procedures involving infectious virus in the APP are within sealed pipes or vessels i.e. under primary containment. When the growth of virus is judged to have reached the optimal stage it is inactivated by the addition of binary ethyleneimine (BEI). The suspension is then transferred through a sealed pipe to a 4,000 litre vessel in the Downsteam Processing Unit (DPU) where the inactivation with BEI continues. (The pipe from the VCU to the DPU passes through the interior of the CPU but is sealed and has expansion points at each end to tolerate expansion during steam sterilization). The virus inactivation process and its verification are carried out and monitored according to the requirements of the European Pharmacopoeia for each individual batch of antigen. The inactivated antigen is concentrated and purified in the DPU and containers with inactivated antigen are passed out of the building through a dunk tank containing a solution of sodium hydroxide (NaOH). The level of the NaOH solution in the tank is monitored and the solution is replaced weekly.

The container with concentrated, inactivated FMD antigen is transported to ID-Lelystad at Edelhertweg (approx 5 km away) where it is stored at ultra-low temperature and, upon request, formulated into vaccine and bottled. Measures are taken to minimize the risk of entry of extraneous microbial agents into this facility including restricted entry of personnel, an air lock at the entrance and maintenance of positive air pressure compared to atmosphere.

Supporting the APP, and located in CIDC-Lelystad HCU (Appendix 2), is a research and development (R & D) Group (2.42.080, 2.43.081, 2.43.082, 2.43.083, 2.43.084 and 2.45.092) and a quality control (QC) Group (2.45.070, 2.45.071, 2.45.072, 2.45.073, 2.45.074, 2.45.081, 2.45.082, 2.45.083 and 2.45.086). In the R & D Laboratory small scale experiments related to strain adaptation and method development are performed. For these purposes

disposable flasks or small scale fermentors (up to 1 litre) are used. "Open" handling with small volumes of virus are only performed in laminar air flow cabinets and culture systems are disinfected with acid solutions before cleansing and sterilisation. For large scale experiments a large fermentor (20 litre), constructed from stainless steel, is used. Steam is used to decontaminate tube connections and sampling ports. In the QC Laboratory tests are performed to verify FMD virus inactivation efficiency, FMD potency tests by serology (virus neutralisation test: VNT) 146s estimation, sterility tests (fungi and bacteria), safety tests (*in vitro*) and confirmation of serotype identity (enzyme-linked immunoassay: ELISA). In this laboratory the quantities of FMDV-material handled are small and any "open" handling is performed within laminar air flow cabinets. Containers and other items are disinfected with an acid solution before cleansing and sterilization.

It is important to point out that personnel operating within a GMP system of quality control must be qualified and properly trained. Currently, 7 operators are employed in the APP and its associated facilities, (2-3 for Technical Services, QA and staff, 5 QC employees and 5-6 R&D employees). All staff meet the requirements of GMP. They are also experienced in the biosecurity rules that pertain to CIDC-Lelystad, including the APP.

4. List of meetings and visits

The people interviewed and visits made during the mission in Lelystad are given in Appendix 4.

5. What are the (safety) risks of selling the FMD antigen production plant in Lelystad?

5.1 Compare the next situations

5.1.1 Use as in 2006 versus no use of the plant at all

Base-line comparator

In order to be able to compare the risk of various possible future uses of the APP, or the change in risk if it were to be taken out of operation entirely, a risk analysis was made of the activities at CIDC-Lelystad HCU, including the APP, during 2004/2005/early 2006 to establish a base-line comparator. During that period the APP was being used to produce FMD antigen for both the Ministry and Intervet. The contract with Intervet ceased on 31 March 2006 and after that date the activities of the APP declined dramatically. For example, during 2004/2005/early 2006, around 70 batches of antigen per year were produced but after 31 March 2006, when the contract with Intervet ceased, the number of

batches declined to around 5/year. The Commission was informed that the maximum production capacity of the APP is estimated to be around 90-130 batches/year (equivalent to 30 - 70 million doses) depending on whether the level of operation was "standard" or round-the clock i.e. full 24 hr.

The risks associated with the operation of the HCU (APP and all other activities) during the comparator period are given in Table 1 in descending order and it can be seen that the greatest challenge to the biosecurity systems was associated with activity 1, the infection of animals with FMD virus in the animal isolation facilities in the HCU. By comparison, the challenge to the containment systems associated with other APP activities was much lower and ranked as medium to low (i.e. activity 3), low (i.e. activity 4 and 5) or extremely low (i.e. activities no. 6, 7, 8 and 9).

The hazard associated with activity 1 would have been especially high when pigs were infected with FMD virus. This is because pigs in the acute stage of FMD excrete very high quantities of airborne virus in their breath. With some strains of FMD virus this can be up to $10^{8.6}$ ID_{50} per pig per 24 hours. By contrast the maximum amount of virus excreted by a bovine animal in 24 hours is $10^{5.1}$ ID_{50}. In other words, a pig can excrete as much airborne virus as around 3,000 cattle.

In the past, animal challenge was done only for authorisation purposes using vaccines produced in the APP. Vaccines produced for routine purposes were normally tested indirectly by vaccinating pigs or cattle and then testing their serological response using *in vitro* assays (VNT). Such animals were not exposed to FMD virus and so these experiments were not carried out in the HCU animal facilities. Cattle were the species generally used when it was necessary to challenge animals with virus. Since 2004, sixteen challenge experiments were performed by the APP as part of registration procedures (draft of a new EU compliant FMD vaccine registration dossier in order to update the marketing authorisation). Challenge experiments were performed for each FMD strain relevant to the LNV vaccine bank (Dutch Ministry of Agriculture). These challenge experiments were performed in cattle except for one FMD virus strain where the potency study (consisting of two PD_{50} experiments) in 2006 was performed in pigs.

By contrast, during the last 10 years around 25 animal experiments were performed by CIDC researchers and of these an average of 2 experiments per year were performed with pigs.

Table 1. Risk analysis of activities at CIDC, including the VPP, during 2004/2005/early 2006.

Activity No.	Activity[1]	Hazard	Challenge to the biosecurity systems	Risk Management[2]	Comment
1	Challenge of susceptible animals with live FMDV in the animal isolation rooms of the HCU.	Heavy contamination of air and effluent in animal rooms. Direct contamination of personnel entering the animal rooms.	Very high	Secondary biosecurity containment.	This activity generates the greatest challenge by far to the containment systems.
2	Challenge of susceptible animals with non-FMDV viruses/microbes in the animal isolation rooms of the HCU.	Heavy contamination of animal rooms. Direct contamination of personnel entering the animal rooms.	Medium	Secondary biosecurity containment.	Non-FMDV viruses/microbes do not present as high a challenge as FMDV.
3	R & D work on FMDV for the VPP in the laboratory section of the HCU.	Breakage, spillage or aerosols from large volume vessels containing high titre FMDV. Contamination of personnel.	Low to medium	Avoidance of breakage and spillage. Secondary biosecurity containment.	This activity has the potential to generate the second greatest challenge to the containment systems associated with the VPP.
4	FMDV research or diagnostic work in the laboratory section of the HCU not associated with the VPP.	Breakage, spillage or aerosols from containers with high titre FMDV. Contamination of personnel.	Low	Avoidance of breakage and spillage. Secondary biosecurity containment.	
5	Addition of seed FMDV to culture vessel in the virus culture unit of the VPP.	Spillage or aerosols from high titre suspensions of FMDV. Contamination of	Low	Avoidance of breakage and spillage. Secondary biosecurity	This is the only activity within the VPP where virus is manipulated outside a vessel or tube.

		personnel.		containment.	
6	Growth of FMDV in virus culture unit of the VPP.	Spillage or aerosols from vessels with large volumes of high titre FMDV. Contamination of personnel.	Extremely low	Primary (closed system) and secondary biosecurity containment.	
7	Quality control tests on FMD antigens for the VPP in the laboratory section of the HCU.	Manipulation of FMD antigens that may not be fully inactivated.	Extremely low	Avoidance of breakage and spillage. Secondary biosecurity containment.	
8	Concentration of FMD antigen in downstream production unit of the VPP.	Manipulation of FMD antigens that may not be fully inactivated. Contamination of personnel.	Extremely low	Primary (closed system) and secondary biosecurity containment.	
9	Research or diagnostic work on non-FMDV in the laboratory section of the HCU not associated with the VPP.	Breakage, spillage or aerosols from containers with high titre of highly contagious viruses/microbes. Contamination of personnel.	Extremely low	Avoidance of breakage and spillage. Secondary biosecurity containment.	

[1] This Table summaries, in descending order, the potential virus challenge to the containment systems when various activities are performed at CIDC-Lelystad, including the VPP.

[2] The essential elements of secondary containment are single HEPA filters on the in-flowing air supply and double HEPA filters on the extracted air. The air pressure within the containment area is maintained at negative to atmosphere. Effluent water and solid waste material are treated to ensure the destruction of virus. Showering by personnel and compliance with quarantine are also important risk management procedures that are relevant to all activities. Primary containment is achieved at the source by safe microbiological techniques and the use of laminar air flow cabinets.

No use at all versus base-line comparator

If the operation of the APP was totally stopped the hazards associated with activities 1, 3, 5, 6, 7 and 8 (Table 1) would cease. As previously stated, the most hazardous of these is activity 1. However, if the APP ceased to operate it is theoretically possible that there could be an uptake of the spare animal isolation room capacity by CIDC-Lelystad for research studies and contract work on behalf of outside companies/others. Some of these experiments might involve FMD virus and possibly even pigs. Therefore, the cessation of the operations of the APP would not necessarily reduce the hazard from animal challenge activities at CIDC. On the contrary, it is theoretically possible that the hazard might be increased, and to an extent depending on the intensity of the FMD-research programme of CIDC-Lelystad.

Since the animal isolation facilities in the HCU have been designed to effectively contain FMD virus and have been tested under severe challenge conditions many times in the past, there is no reason to suppose that the biosecurity containment systems would not perform effectively if challenged more often in the future, including when experiments are performed with FMD virus in pigs. The critical risk management requirements would be to ensure that the biosecurity containment systems are regularly checked and maintained, in particular the air handling and effluent treatment systems, and quarantine periods for personnel strictly maintained. In the case of increased use the HEPA filters would probably need to be replaced more often and it could be expected that the potential for the effluent treatment system to be blocked more often would increase. It would also be important to ensure that the emergency diesel generator is well maintained so that it operates effectively when the hazard level is high.

For all of the activities listed in Table 1 there was a potential hazard that personnel could have been contaminated. This was most probable for activity 1 where the personnel were in direct contact with infected animals and in an environment that was probably heavily contaminated. The risks resulting from these hazards were managed by the wearing of protective clothes and gloves, the disinfection and washing of protective overalls, the washing of exposed parts i.e. face and hands, changing clothes, showering and quarantine period of 3 days before contacting FMD-susceptible animals or visiting premises with such animals.

The reliability of the risk management procedures relating to personnel depends on whether the staff comply with the requirements. There is the possibility of human error or deliberate infringement of the rules. The threat of various sanctions such as dismissal can be applied to ensure compliance but ultimately much depends on the responsibility of the individual and their understanding of the biosecurity measurements, their loyalty and attitude towards the responsibility for the safe operation of the HCU.

The overall conclusion of the Commission is that in the case of no use of the APP for the production of FMD-vaccines the biosecurity risk would decrease moderately (fewer low-risk activities) or significantly when only a few experiments with FMDV-infected cattle are done each year. However, a small increase in animal experiments with FMD-infected pigs for non-APP purposes (e.g. statutory tasks) would increase the challenge to the HCU security systems. However, these were designed and maintained to contain this challenge effectively and have proven to be adequate.

5.1.2 Use as in 2006 versus a commercial exploitation of the FMD antigen production plant by a private company

It is not possible to predict with any degree of certainty what changes a new owner might instigate in the APP. It can, however, be speculated that the effect on the risk profile could be altered by three main factors: (i) an increase in the number of batches of antigen/vaccine produced; (ii) an increase in the activities associated with antigen/vaccine production; and (iii) a change in the quality of the personnel.

If the amount of vaccine production increased then, compared to the situation in 2004/2005/early 2006, the potential hazards associated with activities no 1, 3, 5, 6, 7 and 8 will probably increase. As previously stated, the most significant of these hazards is activity 1 since it will increase whereas the hazards associated with the other activities are only theoretical possibilities. If the amount of animal challenge work associated with the APP increased this might actually reduce the overall risk from the HCU since cattle are the species most likely to be used for vaccine tests. This is because the increased occupancy of the animal facilities by APP for challenge tests, most probably in cattle, would reduce the opportunity for CICD-Lelystad personnel to perform experiments on pigs which are a far greater hazard – as previously stated, one additional experiment involving FMD-infected pigs could equate to 3000 experiments with cattle when the amount of airborne FMD virus excretion is considered.

With regard to the second greatest hazard (activity 3), the Commission was informed that in recent years the work in the R & D Laboratory was focussed mainly on the adaptation of FMD virus strains and other small scale experiments. In the past the number of R & D experiments was not related to the production rate and a change in ownership may not, therefore, result in an increased hazard associated with the R & D Laboratory. But here again, it is not possible to make definite predictions.

A change in ownership and a resulting increase in the other activities associated with the APP i.e. no 3, 5, 6, 7 and 8 in Table 1, would not be expected to produce a significant change in the risk profile compared to the baseline comparator since the hazard rating of all of these activities is low or extremely low.

If the new owners decided to recruit the personnel currently employed in the APP it is probable that the demands on them to produce more batches of vaccine

would increase. However, there is no reason to suppose that this will change the risk profile since these personnel are well-trained and experienced, in particular with the biosecurity rules and GMP compliance requirements. The role of the BSO will be critical in ensuring that the new management does not attempt to cut corners and compromise biosecurity. To ensure that this does not occur the authority of the BSO in regard to the behaviour of personnel employed in the APP must be specified in the terms of the contract between ID-Lelystad Inc. and the Third Party. This would include the right of the BSO to have full access rights to the APP and associated facilities at all times and if he considers that a breach of biosecurity is threatened or has taken place to immediately suspend activities when circumstances require such action until the issue is fully investigated and settled by the interested parties. The BSO should inform the Director of CIDC-Lelystad without delay.

New personnel will not necessarily be experienced in GMP and biosafety. Through intensive training (external and on the job) new personnel could qualify to operate within the GMP processes. Pending qualification new personnel will be only allowed to work under the supervision of experienced staff. Compliance with GMP will be warranted under normal circumstances by frequent internal audits from internal QA staff and external audits by the responsible authorities. This will be a responsibility of the future management.

A situation of concern would arise, however, if the new owner or new personnel did not have the degree of understanding and appreciation of the requirements of biosecurity and GMP compliance that currently exists. The risk management actions that could be taken in this regard would be to specify in the contract the requirement for personnel to comply with the biosecurity regulations and GMP (as in the paragraph above). Furthermore, it should be a contractual obligation for the Third Party to provide personal details about their employees to the Director of CIDC-Lelystad and a contractual right for the Director to request a security check by the the General Intelligence and Security Service if he considers this necessary. The contract should also state that Dutch employment law should apply to the terms and conditions of personnel working in the APP and associated facilities.

5.1.3 Use as in 2006 versus use of the facilities for other purposes with highly contagious viruses/microbes

Whether the APP could be used as currently operated for the production of antigens/vaccines from other highly contagious viruses/microbes would depend on the attitude of the Dutch Veterinary Medicinal Products Unit (BD) to risk aversion. The Commission is of the opinion that the hazard of products in the APP becoming contaminated by FMD virus from other parts of the HCU is extremely low and that management procedures should eliminate the risk.

The following is a worst case theoretical scenario. A power failure affects the animal houses containing FMD-infected pigs and this leads to a positive air pressure situation and an increase of airborne virus concentration. There is a

reflux of FMDV aerosols through doorways to the exterior of the building. The nearby APP, which has continued to operate and so is negative to atmosphere, acts as a giant vacuum cleaner and some of airborne FMD virus is drawn into the building when the doors are opened. (The air inlets to the APP are HEPA filter protected). There are then two possible hazards for the APP: (i) contamination of the product in preparation; or (ii) contamination of the environment, the personnel and perhaps the outside of containers into which the product will be placed.

The risk of contamination, as speculated above, is extremely low and could be managed by using procedures that would inactivate both the non-FMD antigen and any FMD virus that might be present. The routine step of dunking of the flask containing concentrated antigen in NaOH as it is passed out of the APP should inactivate any FMD virus on the outside. An additional measure would be to test the product for the absence of FMD virus. The Commission recognises that despite these risk management procedures it is likely that there could still be a negative perception of vaccines intended for international markets which are produced in an FMD-plant.

The Commission considered another approach which would be to change the production from one microbial agent to another i.e. to alternate production between FMD antigen and that of another highly contagious virus/microbe antigen. However, this would require complete disinfection of both the equipment and the rooms between "runs" and we were informed that this would not be feasible as a routine activity. Even if this were to be done there would still be the risk of contamination of the non-FMD antigen with FMD virus as mentioned above.

The risk of FMD in the situations above is probably extraordinarily low, however, the Commission **recommends** that if the new owner of the APP wants to start the development and production of vaccines under the hypothetical conditions outlined, he/she should consult the Dutch Veterinary Medicinal Products Unit (BD) for an expert opinion about the likelihood of marketing authorisation being granted for vaccines produced under the hypothetical conditions outlined.

An important consideration is that the current GMP license (part relating to the Houtribweg location) is for FMD antigens only and so a change to another agent will not be covered by the existing GMP license and will create the need to make a fresh application.

5.1.4 Use as in 2006 versus use of the facilities plant for other purposes without highly contagious viruses/microbes

If the air handling system for the APP was altered so that the air pressure inside the building was made positive compared to atmosphere the risk of the entry of FMD virus would be greatly reduced and it would then be possible to employ the APP for other purposes using viruses/microbes that are not highly contagious for livestock species. The Commission was informed that this would be technically feasible but before it was done the entire building would have to be fumigated

and for this to be done properly a huge part of the interior would have to be dismantled. Also, since FMD virus would still be handled in other parts of the HCU additional risk management procedures would be required to prevent its entry. This would include an airlock on the entrance to the APP and particular attention to the biosecurity restrictions placed on personnel to ensure that they did not act as a vehicle for the transport of highly contagious viruses/microbes. When these risk management procedures are in operation it would be feasible to produce vaccines in the APP for use in non-FMD-susceptible animals like horses, cats, dogs, poultry or humans. However, changes such as these would result in a reassessment of the current GMP accreditation and the need to reapply under the changed operating procedures. A change to the production of vaccines for use in humans would require additional equipment and procedures to prevent the infection of personnel. It is the Commission's opinion that the biosafety risks related to this situation would be lower. An additional risk management option would be to require any product produced in the APP to be tested for the absence of live FMD virus.

The Commission **recommends** that if the new owner of the APP wants to start the development and production of vaccines under the hypothetical conditions outlined, that he/she consults the Dutch Veterinary Medicinal Products Unit (BD) for an expert opinion about the likelihood of marketing authorisation being granted for vaccines produced under the hypothetical conditions outlined above.

If the production of vaccines using highly contagious human micro-organisms is considered the Commission recommends that expert advice is also sought from the GMP inspectorate of the National GMP Board of the Ministry of Public Health about the requirements for protection of personnel and the consequences for GMP.

5.2 What will be necessary to limit the safety risks to a minimum? Are modifications of the building necessary? And which recommendations can you give for modifications?

As has been stated previously (Section 5.1.2), it is the opinion of the Commission that the contract offered by ID-Lelystad Inc. must clearly stipulate the authority and freedom of movement empowered to the BSO. If the BSO is not satisfied with the actions taken by the Director of CIDC-Lelystad he has the authority to go to a higher authority at the Ministry of Agriculture and recommend that he takes the required actions. The contract must also state that the new owner will ensure that the APP continues to operate according to GMP standards. This is important because GMP provides the additional safeguard that personnel must be qualified and properly trained, that well described and validated procedures are followed and that equipment and installations are well maintained and validated. Furthermore it guarantees that procedures describing the release of antigens from the APP are followed and that authorisation by a qualified person is obligatory.

If the APP is used to produce FMD antigen under the same operating procedures as were described for operation during 2004/2005/early 2006 the Commission sees no need for modifications to the building, at least in the immediate and short term. However, in the medium to longer term the new owner might be interested in consolidating his activities in the APP and having a greater degree of independence. There is space to do this in the floor above the APP which currently is empty. The services to this floor were disconnected many years ago and it has been standing idle since. The major elements of the structure are sound and so it could be refurbished, modified and brought back into use. There would be adequate space to allow the R & D and QC Groups in the HCU at CIDC-Lelystad to be combined on this floor. The new owner might also be interested in creating a formulation and bottling facility in this area instead of using the facilities at ID-Lelystad, Edelhertweg. Another installation that would provide a greater degree of independence for the new owner would be a standby emergency generator.

The cost of refurbishment and installing the necessary biosecurity and other services in the floor above the APP would be substantial. It was pointed out to the Commission that specialist services would be required to remove asbestos from the roof space. Again, this would be a costly procedure.

The Commission **recommends** that the contract offered by ID-Lelystad should give the new owner the option to modify and refurbish the upper floor of the APP by CIDC-Lelystad/ DLO Foundation, under the condition of adaptation of the costs of renting. This should be conditional on the biosecurity regulations and GMP being extended to those areas and remaining at the same standard as for the rest of the HCU.

5.3 Can you describe several scenarios of different potential buyers of the plant, in relation to safety risks?

The most desirable scenario would be the purchase of the APP by a company with an international reputation and experience in the manufacture of FMD vaccines or other highly contagious viruses/microbes according to the GMP standards. Such a company would have a good understanding of the biosecurity hazards associated with the handling of FMD virus and of the requirements of GMP, especially with regard to the need for employees to be suitably qualified and trained. This situation would present the minimum risk.

A company intending to manufacture FMD vaccine, without previous experience of that activity, but possibly having experience of the manufacture of other vaccines (e.g. vaccines for cats, dogs, horses etc) according to GMP, would be obliged to employ the existing personnel in order to obtain FMD "know how" and comply with the GMP requirements. This situation should not significantly change the level of risk.

An intended buyer not experienced with FMD vaccine production or the requirements of GMP but possibly wishing to acquire GMP status in order to

raise his "image" or market position would present a potential risk. This type of owner might agree to the terms of the contract and employ the existing personnel in order to comply with the biosecurity and GMP conditions in the short term but intend in the medium or longer term to sell the APP or change the operations and permit lower standards of operation. The risk of this happening could be managed by including in the contract the condition that if the owner intends to make any change to the operating procedures which could influence the biosecurity that this must be discussed and agreed in advance with the Director of CIDC who has responsibility for the maintenance of biosecurity at all parts and uses of the HCU. If the Director is not prepared to approve the proposed change and there is a dispute he must has the right to advise ID-Lelystad Inc. to terminate the contract.

5.4 What will be the increase in risks that the facilities in a new situation will be exploited for or targeted by terrorist activities? Can you put these risks in perspective of the current situation and other international possible risks of bio-terrorism?

In recent year several countries, including for example the United Kingdom and The Netherlands, have suffered epidemics of virus disease in their livestock populations. Control and eradication required the slaughter of large numbers of animals and the costs for the agricultural sector and taxpayer were enormous. These events were well publicised in the media and there is concern that terrorists might be attracted to the possibility of deliberately starting outbreaks in the future.

FMD virus is handled in the APP and so it is a potential target for bio-terrorists as a source for the virus. A bio-terrorist could either obtain the virus by breaking into and stealing an aliquot of infectious material or else by infiltrating personnel and removing an aliquot surreptitiously. Unauthorised entry to the APP would be difficult as there are several barriers including the need to obtain an electronic pass to open the barrier at reception and the door into the APP. Knowledge of where the virus is stored would also be required. It is very unlikely that a casual intruder would find FMD virus by chance. A person who has infiltrated would have the required knowledge but the Commission concluded that the risk was very low that a company sympathetic to bio-terrorist activities or interested in assisting such activities would go to the length of purchasing or infiltrating a FMD vaccine production facility in order to gain access to the virus. The strains of FMD virus used in the APP have been characterised and the stocks supply is catalogued and audited. While this does not guarantee that a member of the staff could not remove a small aliquot, the Commission was of the opinion that obtaining FMD virus from an outbreak in an endemically infected country would be a much easier option and therefore a more probable scenario.

Nevertheless there is the possibility of infiltration through recruitment and this is why the Commission **recommended** under 5.1.2 that the Director of CIDC should have the right to consult and seek the advice of the General Intelligence

and Security Service for possible screening of the company or its employees if he is concerned about any possible risk to security.

FMD virus has been considered as a potential candidate for bio-terrorist activities because of the devastating effects it could produce. However, these would largely be economic and mainly involve the rural sector. The Commission is of the opinion that microbial agents that cause disease in humans are probably more attractive to bio-terrorists because they have the potential to impact on a wider spectrum of the human population and therefore to cause more terror.

The Commission recommends that in the light of the prevailing international threat of bio-terrorism that the security of all biological institutes in the Netherlands, including CIDC and ASG, are subjected to biosecurity reviews.

5.5 Can you compare the risks also with situation in other countries?

The situation in Pirbright, UK has many similarities to those at CIDC-Lelystad. The development of the BHK-21 cell suspension system at the Animal Virus Research Insitute (AVRI), Pirbright in 1961 offered certain advantages over the earlier Frenkel method for the large-scale production of FMD vaccines. The UK Government was keen to see the method exploited by the private sector and so it decided to allow AVRI to tender the technological "know how", equipment and rental of nearby buildings and installations. The Wellcome Foundation Limited was the successful bidder and in 1961 started work on the establishment of a FMD production laboratory within the perimeter of the AVRI, Pirbright.

During the intervening 46 years a series of companies including, Wellcome Biotechnology, Coopers Animal Health, Pitman Moore and Merial have rented the facilities at Pirbright to produce FMD vaccine. Progressively, over the years the connections between the Institute for Animal Health (IAH; formerly the AVRI) and the commercial vaccine production plant at Pirbright have been separated. For example, initially steam was delivered from IAH's central boiler unit to the vaccine production plant but the latter now has its own steam generator and so the supply from IAH is only provided as a backup. Waste water is still taken from the vaccine plant and heat treated by IAH but the vaccine plant (currently rented to the Merial FMD Laboratory) has its own solid waste and laundry treatment systems.

R & D activities, QC activities, formulation and bottling are all carried out within buildings that are part of or adjacent to the Merial FMD Laboratory. However, any work involving the use of large animals is carried out by Merial personnel in isolation facilities belonging to IAH, Pirbright and rented to Merial for the purpose. Both IAH, Pirbright and the Merial FMD Laboratory have canteen facilities within their respective HCU's but only IAH has a canteen outside the HCU which can be used by personnel from both establishments.

The Merial FMD Laboratory carries out procedures according to the GMP standard and the biosecurity regulations are the same as those at the IAH,

Pirbright. The IAH, BSO is responsible for ensuring that there is compliance with the biosecurity regulations on both sites.

During more than 45 years of operation there have been a number of biosecurity incidents at IAH, Pirbright and the vaccine production laboratory occupied by various companies. However, the Chairman of the Commission, who was Head of IAH, Pirbright for 13 years, is only aware of one serious incident that involved the vaccine production laboratory and this occurred when, due to human error, a valve on a large volume culture vessel was inadvertently opened and 3,000 litre of high titre virus was allowed to discharge into the waste water system. However, this was considered not to represent a serious risk since the infectious material was under primary containment and inactivated when it reached the effluent treatment plant. By contrast, the risk from a single infected bovine animal weighing 500kg, at the peak of disease, and held under isolation conditions, would be far higher since the virus load in the animal (say $10^{7.5}$ ID_{50} compared to say $10^{7.2}$ ID_{50} from the large culture vessel) would probably be of similar magnitude but there would be continuing excretion and secretion of virus into the environment by the infected animal. In the latter case there would also direct challenge by virus to the air filtration system and to personnel.

The low frequency of incidents over a 46 year period at the FMD vaccine plant at Pirbright can be attributed, on the one hand, to the vigilance of the various IAH BSO's who have ensured compliance with the biosecurity regulations, but on the other, to the responsible attitude of the personnel employed by the various private companies. Over the years a significant number of IAH personnel, especially at the senior management level, have been recruited by different companies and this has probably helped to underline the importance of responsible behaviour and compliance with biosecurity requirements. Another factor may be the perception that breaches of discipline are dealt with more severely and expeditiously in the private sector.

All the private companies at Pirbright are well known internationally and have good reputations for ethical behaviour. They all, with one exception, had a record of producing FMD vaccine before coming to Pirbright. Interestingly, the company that had not produced FMD vaccine previously stayed the shortest time.

The Commission considers that the ideal situation would be for new owner of the APP to be an internationally recognised company with a track record of producing FMD vaccines in accordance with GMP requirements. However, it recognises that very few companies fall into this category and so others will have to be considered. In this case the benchmark against which companies are judged should be the contract and so the wording of it will be critical.

The Commission has **recommended** that the contract for the sale and the use of the APP must oblige the new owner to accept certain conditions and these are specified in Section 7.1.

5.6 Where possible, the risks should be qualitatively estimated to permit risk-benefit assessments.

The risks associated with the sale of the APP have been discussed in Section 5.1.1 to 5.1.4. It was concluded that provided the risks are managed by ensuring that there is compliance with the contractual conditions specified in Section 7.1, that the risks should not be a cause for concern even though the amount of activity in the APP and associated facilities would probably increase.

The optimal situation would be for the APP to be sold to an owner who would continue to produce FMD vaccine under GMP conditions. The benefits of this would be:

a) A reduced level of risk compared to 2004/2005/early 2006 due to the challenge of more cattle but fewer pigs with FMD virus. It is not possible to be dogmatic about this as much will depend on the ambitions of the Third Party to perform experiments with FMD-infected pigs and on the research programme of the CIDC (see Section 5.1.2).

b) The maintenance of a critical mass of scientists with experience and knowledge of FMD vaccinology and immunology for scientific and technical discussion, interaction and innovation.

c) The continued availability to the State Veterinary Service of facilities, equipment and knowledge to quickly produce and supply FMD vaccine in the event of a national emergency - if the Third Part accepts that LNV is a preferred client as a condition of the contract.

d) Vaccinated animals are a valuable source of biological materials for research, serological assay development and validation.

e) Contribution to the costs of operating the critical facilities of the HCU.

6. Which problems can we expect with respect to interference between production activities of a new owner and the reference tasks of the CIDC?

6.1 Can you compare the scenarios given under 5.1 for this question?

It is very important that there is no interference between the manufacturing activities of the new owner and the statutory and reference activities of CIDC-Lelystad and steps should be taken to try and prevent even the perception of this occurring. The sensitivity of this issue should be explained to the new owner.

If the APP ceases to operate then this possibility will not occur. If the APP is purchased and used for the production of FMD vaccines or other purposes with or without highly contagious viruses/microbes then it must be ensured that no experiments are done for the private company by CIDC-Lelystad staff. These must only be done by ID-Lelystad staff or by the staff belonging to the private

company. Neither should product registration dossiers of the private party be reviewed nor should the exploitation of CIDC-Lelystad or the HCU be dependent on income from the contract. Overall, therefore, the relations between CIDC-Lelystad and the new owner should be the same as those between CIDC-Lelystad and a random Third Party.

6.2 What recommendations can be given to minimize undesirable interference?

It is **recommended** that if the APP is sold the entrance/reception to CIDC-Lelystad is still used as this guarantees that the same procedures are in force for both employees and visitors to both CIDC and APP. **The option** could be explored of establishing physical separation (barriers) between the APP and CIDC-Lelystad within the site to underline the fact that they are separate enterprises.

It is **recommended** that company signs near the entrance should be no more imposing than those currently in use for CIDC-Lelystad. Any signs on the building should be discrete and not visible from the road.

It is **recommended** that the contract should specify the constraints to be placed on the company about how it will publicise or use for commercial purposes its presence on the site. For example the use of the word "CIDC-Lelystad" should not be used in a way that might be mis-interpreted about a commercial link and should require the permission of the Director of CIDC-Lelystad.

It is **recommended** that only clients and authorised visitors of the Third Party should be permitted to enter the VPP.

7. Under which conditions is a decision to sell acceptable from a risk management point of view?

7.1 If the plant is to be sold to a private company, either for FMD vaccine production or for other purposes, which recommendations can you give us for acceptable conditions?

It is **recommended** that the contract for the sale of the APP must oblige the new owner to accept the following conditions:

a) The contract should state that any disputes or alleged breaches of contract should be settled under Dutch law and that Dutch employment law should apply to the terms and conditions of personnel working in the APP and associated facilities.

b) All of the procedures in the APP and associated facilities must be carried out in accordance with the biosecurity regulations as specified in the CIDC Biosecurity Manual (HCU veiligheidsvoorschrift versie 2004 or future issues).

c) All personnel employed by the private company working in the APP and associated facilities, and any visitors entering those premises, must respect and comply with the biosecurity regulations as specified in the CIDC Biosecurity Manual (HCU veiligheidsvoorschrift versie 2004 or future issues).

d) All of the procedures in the APP and associated facilities must be carried out in accordance with GMP operating standards. (It should be pointed out that GMP compliance requires that personnel are properly qualified and trained).

e) The authority of the BSO must be accepted and it is his right to enter the APP and associated facilities at any time.

f) The BSO has the right to immediately suspend operations in the APP and/or associated facilities if he considers that there has been a breach of the biosecurity regulations or if such a breach is likely or imminent. The BSO must inform the Director of CIDC-Lelystad without delay.

g) The Director of CIDC should have the right to consult and seek the advice of the General Intelligence and Security Service for possible screening of the company or its employees if he is concerned about any possible risks to security. He should also have the right to inform and consult a higher authority at the Ministry of LNV

h) The owner must agree that before he makes any change to the structure or operating procedures of the APP or the associated facilities which might influence the maintenance of biosecurity and/or GMP that he will bring these to the attention of the Director of CIDC-Lelystad and the Biosafety Committee so that the changes can be discussed. If the Director approves the alterations this should be recorded in an addendum to the contract. If changes are made without the agreement of the Director of CIDC-Lelystad he will have the right to advise ID-Lelystad Inc. to terminate the contract and to refuse further use of the HCU by the Third Party.

7.2 Do you have other recommendations or considerations with respect to sale of the FMD production facilities?

The Commission recommends the Minister: (i) to translate the recommendations of the Commission into clear conditions for the sale of the APP to a Third Party and give ID-Lelystad Inc. written notice of these conditions; (ii) to assure that the Minister is fully informed about the conditions under which the APP will be sold to a Third Party; and (iii) will have the right to veto the sale if the conditions described above are not met.

Before 2006 the permit for CIDC-Lelystad to work with all 7 serotypes of FMD virus was issued by the CVO. Since 2006, however, the permit was issued by

the Food and Consumer Product Safety Authority. While formerly the permit was linked to the Veterinary Law and the conditions were explicit, the conditions specified in the more recently issued permit are less clear, in particular with respect to what microbial agents can be handled and in which buildings. The Commission **recommends** that the issuing of permits is reverted to the system that was used previously i.e. the permit is issued by the CVO.

Concern was expressed by personnel at CIDC-Lelystad about the issue of liability in the event that there is a disruption or failure of the services provided to the APP under the SLA. For example, if there is a failure to deliver steam or a power failure at a critical time. The Commission **recommends** that the contract for the sale of and services to the APP is worded in such a way that this issue is anticipated and the potential financial consequences minimised.

8. Appendices

Appendix 1: Terms of Reference.

Appendix 2: Ground plan of HCU at CIDC-Lelystad

Appendix 3: Chart showing the bodies with legal responsibility for the FMD vaccine production plant.

Appendix 4: Meetings and visits during the mission to Lelystad.

Table 1: Risk analysis of activities at CIDC, including the APP, during 2004/2005/early 2006.

9. Acknowledgements

The members of the Commission gratefully acknowledge and thank . . . . . t, ... i, ... s, ... and . . . . . for helpful discussions and constructive advice.

Appendix 1

Terms of reference

Key questions:
1. What are the (safety) risks of selling the FMD vaccine plant in Lelystad?

2. What problems can we expect in relation to the interference between production activities a new owner and the reference tasks of the CIDC?

3. Under which conditions is a decision to sell acceptable from a risk management point of view?

For all questions the focus of the committee shall be on the biosecurity risks, sanitary aspects and necessary restrictions.

Sub questions / elements to be considered:

1. What are the (safety) risks of selling the FMD vaccine plant in Lelystad?

1.a Compare the next situations
- Use as in 2006 versus no use of the plant at all
- Use as in 2006 versus a commercial exploitation of the FMD vaccine plant by a private company
- Use as in 2006 versus use of the facilities for other purposes with highly contagious viruses/microbes
- Use as in 2006 versus use of the facilities plant for other purposes without highly contagious viruses/microbes

1.b What will be necessary to limit the safety risks to a minimum? Are modifications of the building necessary? And which recommendations can you give for modifications?

1.c Can you describe several scenarios of different potential sellers of the plant, in relation to safety risks?

1.d What will be the increase in risks that the facilities in a new situation will be exploited for or targeted by a terrorist activities? Can you put these risks in perspective of the current situation and other international possible risks of bio terrorism?

1.e Can you compare the risks also with situation in other countries?

1.f Where possible, the risks should be qualitatively estimated to permit risk-benefit assessments.

2. Which problems can we expect with respect to interference between production activities of a new owner and the reference tasks of the CIDC?

2.a Can you compare the scenarios given under 1a for this question?

2.b What recommendations can be given to minimize undesirable interference?

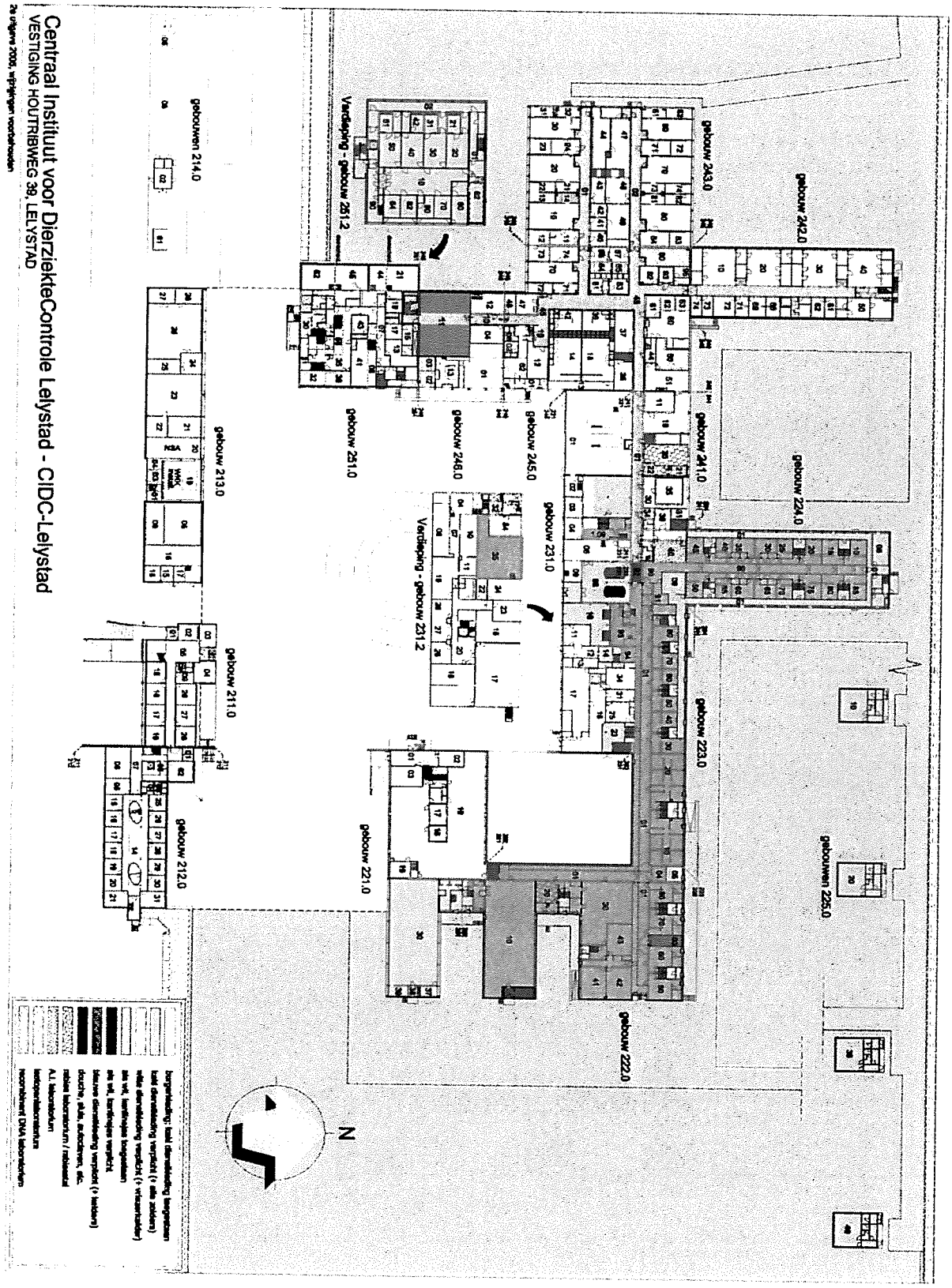
3. Under which conditions is a decision to sell acceptable from a risk management point of view?

3.a If the plant is to be sold to a private company, either for FMD vaccine production or for other purposes, which recommendations can you give us for acceptable conditions?

3.b Do you have other recommendations or considerations with respect to sale of the FMD production facilities?

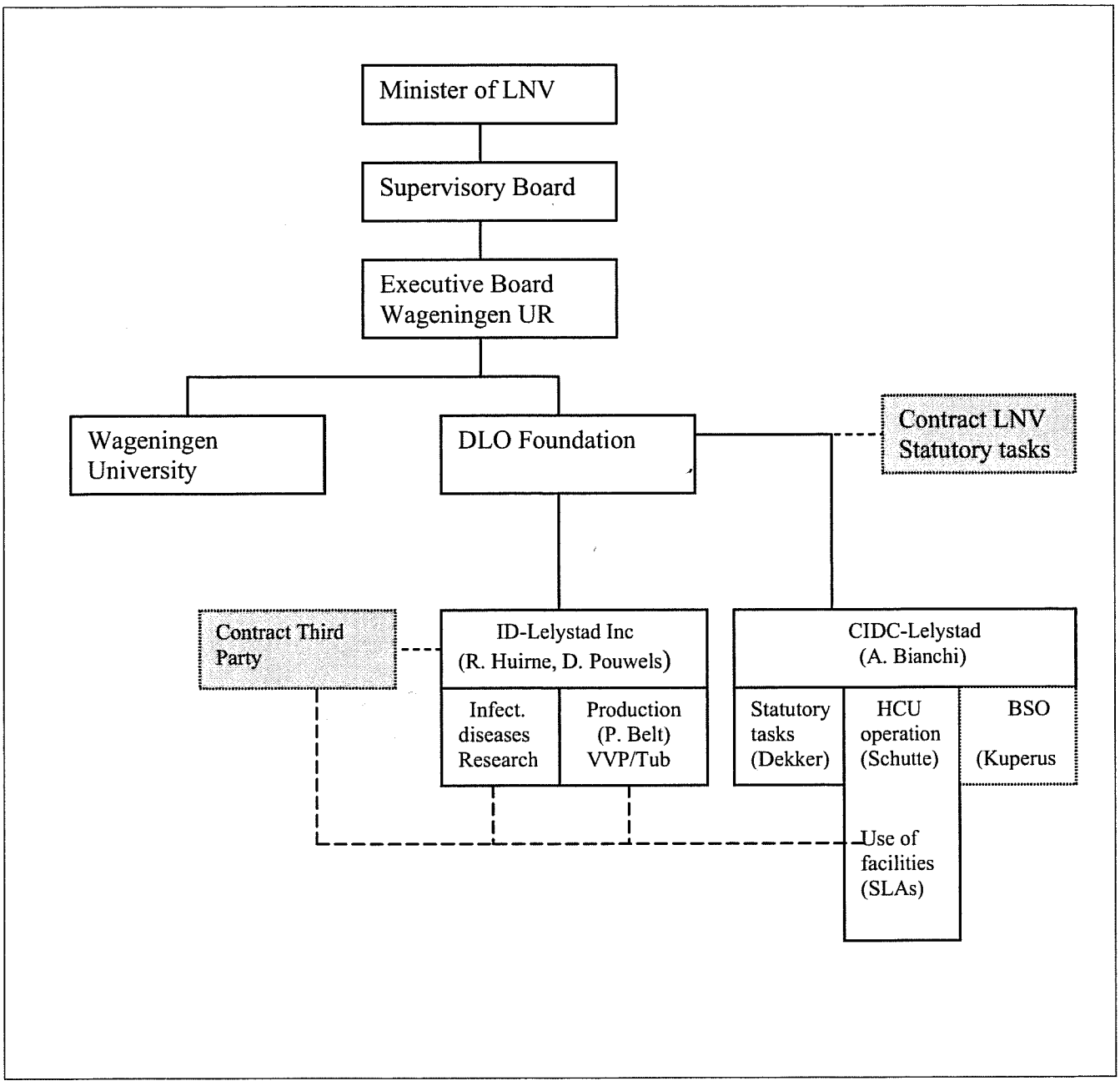
Appendix 2

GROUND PLAN OF HCU, CIDC-LEYLSTAD



APPENDIX 3

Organisational chart showing the bodies with legal responsibility for the FMD Vaccine Production Plant in the HCU of CIDC-Lelystad.



The Department for Animal Sciences of Wageningen University and ID-Lelystad cooperate under the name of the Animal Sciences Group of Wageningen UR.

APPENDIX 4

Meetings and visits during the mission to Lelystad

Wednesday, February 7, 2007

8.30-9.00	start and brief discussion of TOR and approach
9.00-9.20	Introduction to Products Division (ASG)
9.30-10.30	Presentation and discussion on FMD vaccine production
11.00-12.00	Director CIDC- Lelystad
12.00-13.00	Lunch
13.00-14.00	Products Division (continue discussion)
15.30-16.30 (Edelhertweg)	Director ASG

Thursday, February 8, 2007

8.30-12.30	Visit to FMD production facilities Virus Culture and DSP
12.30-13.30	Lunch
13.30-15.00	Facility Manager High Containment Unit
15.00-16.30	Biosafety Officer High Containment Unit

Friday, February 9, 2007

8.30-12.30	Discussion
12.30-13.30	Lunch
14.00-15-00	Research vesicular diseases
15.00-16.00	Director ASG
16.00-17.00	Ministry of Agriculture/CVO