Paul

Ref. 143 F3

26 October 2001

Dr. Joseph Domenech
Director General
CIRAD-EMVT
Campus International Baillarguet
Montpellier Cedex 5
FRANCE

Dear Dr. Domenech

PAN AFRCAN PROGRAMME FOR THE CONTROL OF EPIZOOTICS (PACE)

GRANT CONTRACT FOR A DECENTRALISED PROGRAMME
EUROPEAN COMMISSION EXTERNAL AID
PACE CBPP RESEARCH PROGRAMME

Please find enclosed a copy of the above mentioned Grant Contract duly signed for your records.

Kindly acknowledge receipt.

Yours faithfully

Dr. J.T. Musiime
Ag. DIRECTOR OAU/IBAR

RB/sz

EUROPEAN UNION

DELEGATION OF THE EUROPEAN COMMISSION
TO THE REPUBLIC OF KENYA

Our Ref: BR/4029

23rd October, 2001

Dr. J.T. Musiime
Director a.i./Head of Mission
OAU/IBAR
Maendeleo House
Nairobi

Dear Sir,

Project: **Pan African Control of Epizootics**

Subject: **Grant Contract for a Decentralized Programme**
PACE Research Programme for CBPP

Please find enclosed three copies of the above mentioned Grant Contract duly signed for further transmission.

We will send one copy to the Commission Services for commitment and retain one for our records.

Yours faithfully,

G. Quince

G. Quince
Head of Delegation

Enc: as above

GRANT CONTRACT FOR A DECENTRALISED PROGRAMME EUROPEAN COMMUNITY EXTERNAL AID

PAN-AFRICAN PROGRAMME FOR THE CONTROL OF EPIZOOTICS (PACE)

"CONTAGIOUS BOVINE PLEUROPNEUMONIA (CBPP) PACE RESEARCH PROGRAMME"

European Development Fund project number REG/5007/005
EDF VII & VIII

The Regional Authorizing Officer of the European Development Fund , represented by the Director of the Organization of African Unity Interafrican Bureau of Animal Resources (OAU/IBAR) P.O.Box 30786 Nairobi,("the Contracting Authority")

of the one part,

and

CIRAD-EMVT- Département Elevage et Médécine Vétérinaire du CIRAD-Campus International de Baillarguet-B.P.5035-Montpellier Cedex ("the Beneficiary")

of the other part, have agreed as follows:

Special Conditions

Article 1 - Subject

1(1) The subject of this Contract is a Community grant for the implementation of the operation entitled: Contagious Bovine Pleuropneumonia PACE Research Programme ("the Operation").

1(2) The Beneficiary will be awarded the grant on the terms and conditions set out in this Contract, which consists of these special conditions ("Special Conditions") and their annexes, which the Beneficiary hereby declares he has taken note of and accepts.

1(3) The Beneficiary accepts the grant and undertakes to carry out the Operation under his own responsibility.

Article 2 - Duration of execution

2(1) Implementation of the Operation will begin on:

- the day following that on which the last of the two parties signs

2(2) The Operation's duration of execution, as laid down in Annex I, is 36 months.

Article 3 - Financing the Operation

3(1) The total cost of the Operation eligible for Community financing is estimated at EUR 563,200. as set out in Annex III.

3(2) The Contracting Authority undertakes to provide a maximum of EUR 563,200., equivalent to 100% of the estimated total eligible cost specified in paragraph 1. The final sum will be established in agreement with article 17, Annex II.

Article 4 - Technical and financial reporting and payment arrangements

4(1) Technical and financial reports must be produced to back up payments request in compliance wit article 2 and 15(1) of Annex II.

4(2) Payments will be made in accordance with article 15 of Annex II; of the options referred to in article 15(1) the following will apply:

- advance of 80% of the part of the forecast budget for the first 12 months of implementation financed by the Communities excluding contingencies: 244 000 Euros
- Intermediate annual payment end of Year 1: 126 000 Euros
- Intermediate annual payment end of Year 2: 137 000 Euros
- Forecast final payment of balance (subject to the provisions of Annex II): 56 200 Euros

4(3) Payments will be made into the following bank account:
number: 30004 00640 00010044308 86

holder: Centre International en Recherche Agronomique pour le Développement, Elevage et Médecine Vétérinaire des Pays Tropicaux (CIRAD-EMVT)

address of bank: Banque Nationale de Paris (BNP), rue Maguelonne, 34000 Montpellier France

Article 5 - Contact addresses

Any communication relating to this Contract must be in writing, must state the number and title of the Operation, and must use the following addresses

For the Contracting Authority
Payment requests and the reports attached to them, plus requests for changes to bank account arrangements should be sent to:

Regional Authorizing Officer of the EDF
Director of OAU/IBAR
P O Box 30786
Nairobi, Kenya

Delegation of the European Commission in the Republic of Kenya
Union Insurance Building
Ragati Road
P O Box 45119, Nairobi
Kenya

For the Beneficiary:

CIRAD-EMVT
Campus International de Baillarguet TA30/B
34398 Montpellier Cedex 5
FRANCE

Article 6 - Annexes

6(1) The following documents are annexed to these Special Conditions and form an integral part of the Contract:

Annex I: Description of the Operation

Annex II: General Conditions applicable to European Community grant Contracts for external aid

Annex III: Budget for the Operation

Annex IV: contract-award procedures

Annex V: Standard request for payment and financial identification form

6(2) In the event of a conflict between the provisions of the Annexes and those of the Special Conditions, the provisions of the Special Conditions shall take precedence. In the event of conflict between the provisions of Annexes I, III and IV and those of Annex II, the provisions of Annex II shall take precedence.

Article 7 - Other specific conditions applying to the Operation

The following shall supplement the General Conditions:

7(1) The audit firm which will carry out the audits referred to in article 16(4) of annex II is SOLUSTRO & REYDEL, 8 avenue Delcasse, 75378 Paris, France; tel: 33 1 53 77 38 00.

7 (2) By derogation to article 16(5), the beneficiary will fulfill the obligations referred to in article 16(4) by submitting audit reports specific to the operation carried out by the above mentioned auditor.

7(2) By derogation from Article 2.4 of Annex II (General Conditions) the Beneficiary will provide, in addition to the reports mentioned therein, brief (max 5 pages) technical progress reports on a six-monthly basis to the PACE Programme Co-ordination Unit at OAU/IBAR, P O Box 30786, Nairobi, Kenya.

Done at Nairobi in four originals in the English language, one original being for the Contracting Authority, two originals being for the European Commission and one original being for the Beneficiary.

For the Beneficiary	For the Contracting Authority
Dr Joseph Domenech Director General CIRA-EMVT Campus International Baillarguet Montpellier Cedex 5 France	Dr J T Musiime Regional Authorizing Officer OAU-IBAR Maendeleo House Nairobi
Signature P.O. Bourza Dr. D. BOURZAT CIRAD East African Representative	Signature
Date 12.10.2001	Date 15/10/2001

ORGANIZATION OF AFRICAN UNITY
INTERAFRICAN BUREAU FOR ANIMAL RESOURCES
NAIROBI
OAU/IBAR

Endorsed for funding by the European Commission

Head of the Delegation of the European Commission in the Republic of Kenya
RAGATI Road Nairobi
Mr G Quince

DELEGATION OF THE EUROPEAN COMMISSION
EUROPEAN DEVELOPMENT FUND

Signature

Date 23/10/01

BL

Annex I Description of the Operation:

Contagious Bovine Pleuropneumonia Research Programme: Vaccine evaluation and development of new vaccines and new diagnostic tests

A. SUMMARY

This research programme uses funds from the PACE Programme to improve current vaccines and lay the ground work for development of novel vaccines and diagnostics assays to control contagious bovine pleuropneumonia (CBPP), a fatal disease that limits the cattle industry in most of Africa. The existing control methods, based on restriction of cattle movement and slaughter, are not practical due to cost and cultural practices. The available live attenuated vaccines have a limited duration of immunity and low efficacy. Similarly, diagnostic assays detect antibodies only in the early stages of infection. The proposal will focus on improving the existing vaccines, defining the protective immune mechanisms and to use this information to identify candidate genes for development novel control technologies and the validation of available diagnostic tools.

1. PROJECT TITLE

"Contagious Bovine Pleuropneumonia PACE research programme: Vaccine evaluation and development of new vaccines and new diagnostic tests "

2. PROJECT OVERALL OBJECTIVE

To enhance the performance of the cattle industry in Africa

3. PROJECT PURPOSE

Provide the scientific community, as well to the African veterinary services, techniques (sustainable vaccines and diagnostics tools) for the improvement of control strategies against CBPP.

4. IMPLEMENTING AGENCY

Cirad-Emvt, **World Reference Laboratory for CBPP for the FAO** TA30/G Campus International de Baillarguet 34398 Montpellier Cedex 5 FRANCE. The research will be conducted on a collaborative basis between Advanced Research Institutes in Europe, African National Agricultural Research Systems and ILRI.

5. KEY OUTPUTS

1. **Recommendation on improved use of existing vaccines (T1/SR and T1/44)**
2. **Identification of candidate vaccines**
3. **Development of improved diagnostic assays**

6. TARGET GROUPS

Livestock-keeping communities, veterinary services in Africa and participating member countries as well as African laboratories

7. AREA COVERAGE

The CBPP endemic areas of the PACE countries.

8. TIME FRAME

36 months duration with projected start date of September 2001

9. PROJECT COST

563 200 EUR

B. PROJECT DESCRIPTION

B-1 Background

Rinderpest having been eradicated from most African countries, contagious bovine pleuropneumonia (CBPP) has been recognized as one of the major infectious disease threatening cattle in the continent. In the recent past, CBPP has reemerged in countries that had succeeded in eradicating it (Kenya, Tanzania, Rwanda, Burundi, Botswana...) and the number of outbreaks seemed to increase dramatically in countries where the disease had been under control, mainly in West and Central Africa. This is the reason why the PACE program has identified CBPP as one of it's priority.

Defining a sound and efficient strategy for CBPP control is not an easy task. It requires first an evaluation of the global economical cost of the disease and, then, to define the type of control measures that can effectively be applied. It also requires to have a true evaluation of the immediate impact of these measures, and an evaluation of their cost. Finally choices will have to be made according to a cost/benefit analysis.

Experience from the past centuries shows that eradication of CBPP can be achieved without the need of any vaccine nor any laboratory diagnostic tool simply by applying strict stamping out measures in affected herds and strict control of animal movements. This is how UK and USA got rid of it at the end of the nineteenth century. This policy was successful for three important reasons: clinical diagnosis was easy because of the lack of any interfeering antibiotic treatment, transmission of CBPP was well understood (direct contact neeeded, no wildlife reservoir, no indirect transmission by fomites) and quite slow unlike viral diseases such as FMD.

More recent examples are also enlightening. Botswana eradicated CBPP very rapidly by a tremendous effort including the slaughter of the whole cattle population in the affected region. This was, and still is, successful because Botswana is able to prevent the introduction of cattle from neighbouring infected countries. In the same part of the continent Namibia is implementing a different strategy based on repeated annual vaccinations. This strategy is successful in controlling the disease but unlikely to achieve eradication as long as infected cattle can enter Northern Namibia. In the 60ies Australia succeded in eradicating CBPP by a

outbreaks by serology (CFT testing) and in the end by a strict slaughter policy. Fourty years later, Australia is still free of CBPP.

The above mentionned examples show that CBPP control strategies can be defined and implemented with success under various circumstances with various means. In all cases however, a strong political will to implement costly measures was observed. In many PACE countries however, CBPP control strategies ought yet to be defined and/or revised.

Means to fight CBPP are well identified: slaughter, vaccination and antibiotic treatments. Means to identify the disease are also well identified: clinical diagnosis, detection of lesions at slaughter houses, laboratory confirmation to identify the agent (MmmSC) and serological analysis with validated tests.

Previous experience in the field or in experimental conditions permit an evaluation of all these tools. What is already known is enough to be able to analyse the CBPP situation of a country and then propose a strategy. This exercise should follow a logical framework (logical tree of decision making: analysis of the problem, evaluation of tools, evaluation of costs, evaluation of different strategies and choice of one according to a goal and budget available, implementation of the strategy, ongoing evaluation of the strategy, continuation, modification or stop of the strategy...). As a development project, the PACE program will enable African veterinary services to assess correctly the importance of CBPP, and design a response.

Research on CBPP is expected to render the control or eradication of the disease more easy and/or economical to achieve. This may be achieved by improving all the tools available or designing new ones. However, funds for the research are very scarce and a definition of priorities as well as a coordination with the work that is done elsewhere are required. Group meetings led by the World Reference Laboratory for CBPP have identified a number of subjects that compose his research programme.

Other important subjects could not however been incorporated in this PACE program. It is the case of epidemiology research and more particularly research on the impact of antibiotic treatment. This is a very important point which has a stong impact on CBPP transmission. The point has to be made that if additional fundings can be found it would be worthwhile studying the impact of antibiotherapy. In the meantime such studies can be performed at the field level within the national PACE components. This should ensure preliminary results to be collected before more detailed studies are performed.

B-2 Purpose

Provide the scientific community, as well to the African veterinary services, techniques (sustainable vaccines and diagnostics tools) for the improvement of control strategies against CBPP in order to enhance the performance of the cattle industry in Africa

B-3. Objectives

1) Define improved conditions of use of the current vaccines, with particular emphasis on the effect of revaccination using T1/44 and T1sr and optimum dose of organisms capable of inducing long lasting immunity.

2) Identify alternative candidate vaccines.

B-4 RESEARCH ACTIVITIES

The project will be conducted by a consortium of two African, two European and one international laboratories with complementary expertise and assets regarding access to experimental premisses and/or advanced technologies. France, Kenya and Cameroon are used to work in close collaboration in the field of CBPP or CCPP research and vaccinae trials. Great Britain and ILRI will join this group and bring their own expertise as an added value. The choice of these partners has been made by Cirad, the world reference center for contagious bovine pleuropneumonia, taking into account their expertise in various scientific fields but also taking into consideration work performed elswhere as to prevent duplication of work. The position of Cirad allows a permanent exchange with other partners and projects and should allow a continuous exchange of scientific information.

The participants of the consortium are

Kenya	Kenya Agricultural Reseach Institute, National veterinary research center, Muguga (KARI)
Cameroon	Laboratoire National Vétérinaire, Garoua (LANAVET)
Great Britain	Moredun Institute (MI)
International	International Livestock Research Institute (ILRI)
France	Centre Interantional en Recherche Agronomique pour le Développement (CIRAD)

This project will be implemented over a three years period.

Experimental trials will be started as soon as possible in Kenya and Cameroon. These trials should allow the rapid determination of key factors affecting the efficacy of the currently used vaccines and notably the effect of initial dosage or the effect of re-vaccination on the final protection after one year. These trials should also allow a finer characterization of the protective immune mechanisms at stake in vaccinated animals as well as provide a number of samples for the validation of newly developped diagnostic tests.

Parallel research will be started as soon as possible in the various laboratories in order to define suitable antigens and techniques for the development of new diagnostic tests. Particular attention will be paid to antigens that trigger a homogneous response in vaccinated animals. Serological tests will be sought because of their userfriendliness but cellular mediated immunity will also have to be analyzed because of the possible role of such response in the case of CBPP pathogenesis and protection.

New candidate vaccines may emerge both from the study of the pathogen itself, for exemple by the identification of virulence genes or as a "by-product" of the search for new diagnostic tests. Particular attention will be paid to genes coding for surface proteins with a key role in mycoplasma adherence, survival or multiplication.

The research which is planed during this PACE program is the direct continuation of the CBPP-EU project and other projects that have already allowed unravelling key factors for future research. This PACE research project will be conducted in parallel with other complementary projects or fundings that will potentiate the results obtained. In that respect

these institutions own budgets. In the case of Cirad, four researchers will be devoted to CBPP research.

The breakdown of financial resources going to the various partners is as follows:

- ILRI: 100000 Euros
- KARI: 127000 Euros
- LANAVET: 112200 Euros
- Moredum: 15000 Euros
- Cirad/Emvt: 179 000 Euros (plus cost of auditors)

4. WORKPACKAGES

WP1 Evaluation of T1/44 and T1sr strains, Dose-effect (LANAVET-Cirad)

Introduction

There is much controversy on the correlation between the vaccinal dose and subsequent protection. Analysis of the literature does not give much clue as most of the trials were performed with live broth vaccines containing variable numbers of mycoplasmas. Furthermore injected doses were containing very often more than 10^8 and up to 10^{10}. The single paper relating experiments that tried to establish a dose response with 10^5, 10^7 or 10^9 viable mycoplasmas gave conflicting results. Even though the challenge was quite mild, complete protection was not achieved even with the 10^9 doses.

With the currently used freeze dried vaccines, the standard vaccine dose that is theoretically injected to animals is rarely much more than 10^7. It is often much less due to bad conservation of the vaccines. The recent vaccine trials in Cameroon and Kenya have shown that this dose is certainly not capable of inducing a satisfactory protection when it is administered into naive animals, for example to protect CBPP free regions that are at high risk of being contaminated. It would therefore be very interesting to check if higher dosages are able do induce a better immunity. Higher dosages could easily be obtained with the current production methodology by reducing the number of doses per vial without modifying the total amount of product in the vial. This procedure would certainly increase the cost of the vaccine but this may be acceptable in view of a possible benefic consequence. Higher doses could possibly be obtained by changing the production methodology but it would then need a specific validation as these modifications may lead to strains with modified characteristics.

Proposed protocol

Doses to control:	10^7, 10^8, 10^9
Strains to use:	T1sr and T1/44
Number of animals per dose:	15 (This is a minimum)
Challenging strain:	8740 used previously in Cameroon
Time of challenge:	Three months after vaccination

Number of animals immunized with T1/44	45 (A4, A5, A6)
Number of animals immunized with T1sr	45 (B4, B5, B6)
Number of animals in the control group:	40 (C2)
Number of animals in the intubated group:	30 (I2)
Total number of animals	160

The protocol would then be strictly similar to what has been done in Cameroon previously. It is expected that the same strain being used, similar numbers of affected cattle will be found in the control group, roughly 85% morbidity and 42% mortality. If the protection afforded by the 10^7 dose is as low as previously observed, any increased protection should be visible with this number of animals. Differences between the groups will be assessed by Chi-square analysis.

Timeframe

Day 0 = receipt of funds by LANAVET
Months 0-3: Selection of suitable animals
Animals being more than 3 years old and not vacinated. This later point being tested by rinderpest serology
Months 3-5: Genetic characterization and allocation to groups
- Blood sampling and extraction of DNA at LANAVET
- Analysis by PCR-RFLP at CIRAD

Months 5-6: Vaccination
- Vaccines to be supplied by CIRAD
- Doses obtained by various dilutions of a mixture of vials (minimum 3)

Months 9: Challenge
- Intubation of 30 animals and follow up of symptoms
- Contact with other groups as soon as symptoms observed

Months 9-12: Follow-up
- Record of symptoms
- Harvest of serum

Month 12-13: Slaughter of surviving animals
- Record of lesions
- Calculation of indexes (Symptoms and lesions)
- Calculation of protection rates

WP2 Evaluation of T1/44 and T1sr strains, boosting effect (KARI-Cirad)

Introduction

Up to now, the indications of use of the CBPP vaccines were the following. In enzootic countries, control of CBPP can be achieved by annual vaccinations of the totality of the bovine population. A good example of this strategy is now the northern part of Namibia where the only remaining foci are imported from neighbouring Angola. In regions that are at high risk of being infected, or in CBPP-free herds surrounded by infected neighbours, it is clear that a single vaccination will not induce a sufficient protection as to prevent the spread of the disease. This has been evidenced recently in Botswana and the past trials in Cameroon and Kenya confirmed that neither strain, T1sr or T1/44, was satisfactory for that matter. FAO recommended that repeated vaccinations were to be done after three months, and nine months after the primary vaccination in order to get a satisfactory level of protection. However there is very little, if any, litterature relating the boosting effect of CBPP vaccines at the dosage of 10^7. Moreover, the last experiments also gave some indications on the protection that could be expected from a revaccination after one year. This protection rose to very satisfactory levels. Therefore it is felt that additionnal experiments should be conducted in order to define a vaccination strategy in case of emergency vaccinations. Naturally a single vaccination will

revaccination after a certain time might be an alternative approach to give an increased immunity level as well as a durable one.
The objective of this trial is therefore to evaluate the optimum timing for a revaccination inducing a longer lasting immunity (here after one year). The revaccination timing were principally chosen according to serological results obtained during the last experiments in Cameroon and Kenya showing a decline of antibody titers after two months.

Proposed protocol

Doses to control: 10^7, once and twice at two and six months interval
Strains to use: T1sr and T1/44
Number of animals per dose: 15 (This is a minimum)
Challenging strain: Local Kenyan strain
Time of challenge: One year after the second vaccination

Number of animals in the T1/44 group: 45 (A1, A2, A3)
Number of animals in the T1sr group: 45 (B1, B2, B3)
Number of animals in the control group: 40 (C1)
(including ten with specified genotype)
Number of animals in the intubated group: 30 (I1)
Additional animals for ILRI's exp. 10 (E1, E2)
Total number of animals 170

This experiment is expected to give an indication whether revaccination provides a satisfactory level of protection after one year when the challenge is performed with a highly virulent strain. Comparisons can be made between the groups vaccinated once or twice in this experiment or with the former experiments.

Satisfactory levels of protection will indicate that one boost may be adequate to increase the level of protection in naive cattle and furthermore if the protection is likely to last more than one year. If not, alternative strategies will have to be found as repeated vaccinations might be seen as too onerous.

Timeframe

Day 0 = receipt of funds by KARI
Months 0-3: Selection of suitable animals
Animals being more than 2 years old and not vacinated. If possible animals not related.
Months 1-3: Characterization and allocation to groups
Months 4: Vaccination
- Vaccines to be supplied by CIRAD (same batches that are used at Lanavet)
- Groups A3 and B3

Months 8: Vaccination
- Groups A2 and B2

Month 10: Vaccination
- All groups (A1, A2, A3, B1, B2, B3)

Months 22: Challenge
- Intubation of 30 animals and follow up of symptoms
- Contact with other groups as soon as symptoms observed

Months 22-25: Follow-up

- Harvest of serum

Month 25-26: Slaughter of surviving animals

- Record of lesions
- Calculation of indexes (Symptoms and lesions)
- Calculation of protection rates

WP3 Search for new vaccines (Cirad-ILRI-KARI-LANAVET)

WP 3.1 evaluation of protective immunity in vaccinated cattle (ILRI)

Animals will be chosen within the groups held in KARI for the T1 trial. Five animals will be chosen randomly in each group but excluding animals bearing potential resistance or sensitivity genetic markers.

Group A2: 5 animals vaccinated once with T1/44 and boosted 2 months later

Group A1: 5 animals vaccinated once with T1/44

Group E1: 5 animals inoculated with 10^8 pathogenic MmmSC strain, treated with long acting tetracyclin as soon as the invading oedema is developping (more than 20cm diameter)

Group E2: 5 animals immunized with washed mycoplasmas (0,2 mg/dose) inactivated by heating at 60° for 15 minutes and mixed with saponin as the adjuvant.

Group C: 5 control animals not treated

Analysis of protective immune responses (post immunization and post challenge)

Serum will be collected from animals in the above groups prior and during immunisation and used in the analysis of specific antibody responses to MmmSC.

PBMC will also be collected and the following assays performed

- FACS analysis to determine the kinetics of the responding cell populations in vivo.
- Establishment of T-cell assay systems: In vitro co-culture of PBMC (depleted of (* T cells) with inactivated Mmm antigens/ monocytes pulsed with live Mmm and then irradiated/ defined Mmm antigens to determine a) antigen specific T-Lymphocyte proliferative responses b) Interferon- (production c) responding T cells will be characterized at the bulk and clonal level for phenotype by FACS analysis and cytokine expression by RT-PCR.

Generation of T cell lines and clones from immunised animals.

A panel of T-cell lines and clones specific for MmmSC will be generated from responding T-cells from protected as well as non-protected animals. These T cells will be characterised by Facs analysis for phenotype, by RT-PCR for cytokine profiles and by ELISA for Interferon- (production. Correlation between the various phenotypes of responding T cells and elimination of infection should be the basis for establishing new tools for screening the different candidate vaccines.

Several approaches will be used to identify potential protective antigens of MmmSC. The first approach will be based on screening of biochemically purified protein molecules from MmmSC (gel filtration using fast performance liquid chromatography, FPLC) using immune sera and T-cell probes to screen

a- defined MmmSC antigens

b- genes from genome analysis

c- cDNA expression libraries for protective antigens using in vitro antigen presentation techniques developed at ILRI.

Expected outputs

- Valuable information on the protective immune mechanisms in CBPP on which future development of subunit vaccines will be based.
- The information on Lymphocyte populations and cytokine profiles will be of tremendous valu in current and future CBPP vaccination campaigns in terms of vaccine success/failure.
- T-cell lines and clones that are generated will be of use in the identification of candidate vaccin antigens either through biochemical fractionation (FPLC), from existing defined antigens, screening of genes from genome analysis and cDNA expression libraries.

WP 3.2 identification of virulence genes in MmmSC and construction of deleted MmmSC strains (Cirad-LANAVET)

. Putative virulence genes will be selected from a sequence bank already made at Cirad from a genomic library obtained from strain 8740, the highly pathogenic strain used in the former trials in Cameroon. Later on, more comprehensive sequence banks should be obtained and allow a wider choice of genes. Genes will be selected according to various criteria for example the comparison with virulence genes identified in the databanks, the identification of genes involved in metabolism but which inactivation should not be lethal to the mycoplasma and simply impair it's growth, genes which should play a role in the mycoplama's ability to evade the bovine immune response.

. A first gene will be selected for it's antigenicity and serve as a marker for inactivation.

. Preliminary constructs of deleted MmmSC strains will be made as to validate the protocol and verify the inactivation of the selected gene.

. Further constructs will then be made with the various selected genes

. The effect of this inactivation will then be tested in LANAVET by subcutaneous inoculation to susceptible cattle. Particular attention will be paid to the development of an invasive oedema (Willems reaction) which is correlated to the virulence of MmmSC strains. The quantification of this oedema will allow a measurement of the attenuation of the strain. The persistance of the strain at the inoculation site will be monitored after slaughter, one month after inoculation. Animals developping an invasive oedema will be treated with antibiotics and slaughtered one month after.

Expected output

A mechanism as to measure the impact of some genes on the virulence of MmmSC strains
Candidate vaccines which are specifically attenuated

WP 3.3 identification of possible protective antigens (Cirad)

. Putative interesting genes will be selected from a sequence bank already made at Cirad from a genomic library obtained from strain 8740, the highly pathogenic strain used in the former trials in Cameroon. Later on, more comprehensive sequence banks should be obtained and allow a wider choice of genes. The choice of genes will be made according to their function and location. Primary targets will be genes expressed at the surface of the mycoplasmas that do play an important role in the survival and the multiplication of the bacteria, such as transport proteins.

. Preliminary characterization of these antigens will be obtained through the synthesis of immunogenic peptides and verification of the location of the antigens by use of rabbit

. Further evaluation of these antigens will be obtained by invitro expression of surface exposed antigens. In vitro expression in commercially available kits may necessitate the use of synthetic genes with adapted codon preferences.

. Preliminary evaluation of these preparations will be made in collaboration with other projects on CBPP as to verify the ability of these preparation to evoke an immune response in terms of antibody production as well as cellular immune response.

Expected outputs

A minimum of ten identified surface antigens, expressed in vitro in totality or partially.
An evaluation of their ability to induce growth inhibiting antibodies
An evaluation of their ability to induce a cellular immune response in bovines

WP4 Search for new diagnostic tests

WP 4.1 evaluation of a penside test (Moredun, KARI)

The need for a rapid diagnostic test has been identified as a priority by various experts during the last FAO/OIE/IAEA consultative meeting in Rome in october 2000. Accordingly this topic has been included in this project.

Promising results were announced at the occasion of the FAO CBPP. The proposed test would be based on coated beads either with capsular polysaccharide (CPS), a major antigenic component of MmmSC strains, or with antibodies directed towards CPS. These tests might be able to detect the blood circulating CPS at an early stage of the disease or to detect antibodies to CPS in later stages of the disease.

The potential of such tests certainly merit to be tested rapidly as the technology is already available. Therefore a budget line will be devoted to the production of a large batch of these reactives in order to make them available for testing during the vaccine experiments.

The validation of this test will be performed through the laboratory network of the IAEA under an RCM project due to end in 2002. The last meeting held in Nairobi in June 2001 allowed the definition of a protocol with a comparison of three tests including the "classical" colored MmmSC antigen. Comparisons wil be made in various countries on experimentally infected animals, in non infected animals or in animals with chronic lesions. Comparisons will be drawn with the curently used tests, the CFT and the cELISA.

WP 4.2 identification of antigens for evaluation of postvaccinal response (Cirad-KARI)

Contrarily to the rinderpest situation, there is no way to monitor the efficacy of the CBPP vaccination campaigns. The seroconversion, observed with the current tests for CBPP, is highly variable from one situation to another and furthermore there is no strict correlation between sero-conversion and protection. Obtaining a test that correlates with a previous immunization of the animals is therefore of vital importance as it would allow the verification that vaccination campaigns are performed correctly. Practically there are numerous factors that can affect the efficacy of the vaccination campaigns, from cheating, bad storage of the vaccines to the use of improper diluents...

. The first option is to identify the most immunodominant antigen that triggers an immune

defined time after vaccination would allow an evaluation of the number of animals that received the vaccine.

. The second option is to develop a test based on the induction of interferon gamma by various antigens. This approach might be more efficient as preliminary results have shown that protection is mediated by a stimulation of CD4 Tcells with an interferon production. In that case such a test would allow an evaluation of the protection afforded and not simply a correlation with vaccine intake.

. Eventually, the development of new vaccines will allow the distinction of vaccinated versus infected animals. In the case of a deleted strain, the deleted immunogenic antigen will be used as a control of infection. In the case of defined antigens a serological test using this antigen will serve as a marker of immunization and other antigens will serve as markers of infection.

Expected output

Identification of ten immunodominant antigens
Evaluation of their ability to be used in an ELISA format
Evaluation of their ability to be used in an Interferon gamma test

WP5 Coordination, travels and workshop

Coordination

This is an essential component as the validity of the vaccine trials depend largely on the possibility to compare the new results with results obtained formerly during the last CBPP-EU project.

The coordination will ensure a continuous flow of information between the various partners. This will be greatly facilitated now that colleagues in Cameroon and Kenya can je joined by E.mail and mobile phones.

An important part of the coordination will also consist in linking this research project with all the projects dealing with CBPP. Care will be taken to maintain links with the PACE coordination unit at Nairobi, the FAO headquarters in Rome and the IAEA in Vienna.

Travels

Vaccine trials in Cameroon and Kenya will necessitate regular bilateral travels with France in order to ensure the availibility of the vaccines, the exchange of biologic material and the consistency of the trials.

Workshop

Paucity of fundings does not allow regular yearly meetings. Instead, a single meeting should be held at the end of year two when the T1 trials are finished. This meeting should be held wether in Nairobi or in Rome. Its objectives will be to issue the final results of T1 vaccine testing that will allow International agencies such as the FAO or the OIE to update recommendations on the use of T1/44 and T1sr. Accordingly these results will be publicized in order to allow veterinary services to be kept informed. Results will be made available through scientific papers but also though internet sites at FAO, OIE or Cirad.
This workshop will also be the occasion of discussing the results in terms of new vaccines and diagnostic tests and allow a re-orientation for the final year of the project.

List of participating institutions

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ANNEX II

General Conditions applicable to European Community grant Contracts for external aid

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GENERAL AND ADMINISTRATIVE PROVISIONS

Article 1 – General obligations

1(1) The Beneficiary shall ensure that the Operation is carried out in accordance with the Description of the Operation contained in Annex 1, either alone or in partnership with one or more NGOs or institutions.

The Beneficiary may subcontract a limited portion of the Operation (works and services), preferably to local firms. The bulk of the Operation must, however, be undertaken by the Beneficiary.

If implementation of the Operation involves the conclusion of contracts by the Beneficiary, the contract-award procedures set out in Annex IV shall apply. The partners, the subcontractors and the supplies must originate in the Community or the country or countries eligible for grants under the programme of which the Operation is part.

The Community recognises no contractual link between itself and the Beneficiary's partner(s) or between itself and a subcontractor. The Beneficiary alone shall be accountable to the Commission for the implementation of the Operation. The Beneficiary undertakes to ensure that the conditions imposed upon him under this Contract also apply to all partners and subcontractors involved.

1(2) The Beneficiary must implement the Operation with the requisite degree of care, efficiency and diligence, as required by best practice in the field concerned, and in compliance with this Contract.

To that end, the Beneficiary shall mobilise all the financial, human and material resources required for full implementation of the project, as specified in the Description of the Operation, endeavouring to use local human and material resources.

1(3) If the Beneficiary or any of the Beneficiary's partners, subcontractors or agents indulges in corrupt practices in connection with this or any other Operation financed by the Commission, the latter may suspend the Operation or terminate the Contract in accordance with Article 11(3).

Article 2 – Obligations regarding information and financial and technical reports

2(1) The Beneficiary must provide the Commission with full information on the implementation of the Operation. To that end, the Beneficiary must draw up intermediate reports and a final report. These reports shall consist of a technical portion and a financial portion. The Commission may request additional information at any time; that information must be supplied within 30 days of the request.

2(2) The Beneficiary must send the Commission intermediate reports in accordance with the provisions below. Every report must provide a complete account of all aspects of implementation for the period covered.

The report shall be laid out in such a way as to allow comparison of the objective(s), the means envisaged or employed, the results expected and obtained and the budget details for the Operation. The report must be accompanied by a plan of action for the next phase of the Operation's implementation.

2(3) The final report must contain a detailed description of the conditions in which the Operation took place, information on the steps taken to identify the Community as the source of financing and on considerations which could be used to evaluate the Operation's impact, a final statement of all the eligible costs of the Operation, plus a full summary of the Operation's income and expenditure and payments received.

2(4) The reports shall be presented in the same language as the Contract and in triplicate. They shall be submitted at the following intervals:

A if payments follow option 1 or option 3 in Article 15(1): a single and final report shall be forwarded to the Commission within six months of the end of the Operation's duration of execution as defined in Article 2 of the Special Conditions;

B if payments follow option 2 in Article 15(1):
- an intermediate report must accompany every request for payment;
- the final report shall be forwarded to the Commission within six months of the end of the Operation's duration of execution as defined in Article 2 of the Special Conditions.

2(5) The Special Conditions may stipulate that the Beneficiary must supply an extra copy of the reports for the Commission Delegation in charge of monitoring the Operation.

2(6) If the Beneficiary fails to supply a final report by the final report deadline laid down in Article 2(4), and fails to furnish an acceptable and sufficient written explanation of the reasons why he is unable to comply with this obligation, the Commission may terminate the Contract in accordance with the first indent of Article 11(3) and recover the sums due.

Furthermore, where payments follow option 2 in Article 15(1) and the Beneficiary fails to present an intermediate report and a request for payment by the end of each twelve-month period following the date laid down in Article 2(1) of the Special Conditions, the Beneficiary must inform the Commission of the reasons why he is unable to do so, and must provide a summary of the state of progress of the Operation. If the Beneficiary fails to comply with this obligation, the Commission may terminate the Contract in accordance with the first indent of Article 11(3) and recover the sums due.

Article 3 - Liability

3(1) The Community cannot under any circumstances or for any reason whatsoever be held liable for damage or injury sustained by the staff or property of the Beneficiary while the Operation is being carried out. The Community cannot therefore accept any claim for compensation or increases in payment in connection with such damage or injury.

3(2) The Beneficiary shall assume sole liability towards third parties, including liability for damage or injury of any kind sustained by them while the Operation is being carried out. The Beneficiary shall discharge the Community of all liability associated with any claim or action brought as a result of an infringement by the Beneficiary or the Beneficiary's employees or individuals for whom those employees are responsible of rules or regulations, or as a result of violation of a third party's rights.

Article 4 – Confusion of interests

The Beneficiary undertakes to take all precautions necessary to avoid confusion of interests and shall inform the Commission immediately of any situation giving rise to or likely to give rise to any such confusion.

Article 5 - Confidentiality

The Commission and the Beneficiary undertake to preserve the confidentiality of the reports referred to in Article 2 and of any document, information or other material communicated to them in confidence.

Article 6 - Publicity

6(1) Unless the Commission requests otherwise, any notice or publication by the Beneficiary concerning the Operation, including at a conference or seminar, must specify that the Operation has received funding from the European Community.

The Beneficiary must take all necessary steps to publicise the fact that the Community has financed or co-financed the Operation. To that end, the Beneficiary shall refer to the Operation and the Community financial contribution in information given to the final recipients of the Operation, in internal and final reports and in any dealings with the media.

6(2) Any publication by the Beneficiary, in whatever form and by whatever medium, including the Internet, must carry the following warning: "This document has been produced with the financial assistance of the European Community. The views expressed herein are those of [name of Beneficiary] and can therefore in no way be taken to reflect the official opinion of the European Community."

Article 7 – Ownership/use of results and equipment

7(1) Ownership, title and industrial and intellectual property rights in the results of the Operation and the reports and other documents relating to it shall vest in the Beneficiary.

7(2) Notwithstanding the provisions of the first paragraph, the Beneficiary shall grant the Commission the right to use freely and as it sees fit all documents deriving from the Operation, whatever their form.

7(3) By the end of the implementation period for the Operation, the equipment, vehicles and supplies paid for by the Community grant must be transferred to any local partners of the Beneficiary or to the final recipients of the Operation. Copies of the title transfers must be attached to the final report.

Article 8 - Evaluation of the Operation

8(1) If the Commission performs an intermediate or subsequent (ex-post) evaluation, the Beneficiary must undertake to provide the Commission or its authorised agents with any document or information likely to help that evaluation to be successfully concluded. The Beneficiary must also provide the Commission or its authorised agents with the access rights described in Article 16(2).

8(2) If one party carries out or commissions an evaluation in the context of the Operation, it must provide the other party with a copy of the evaluation report.

Article 9 - Amendment of the Contract

9(1) Any amendment of the Contract, including the annexes thereto, must be set out in an addendum, to be concluded on the same terms as the original Contract.

If the request for an amendment comes from the Beneficiary, the latter must submit that request to the Commission two months before the amendment is intended to enter into force, except in cases which are duly substantiated by the Beneficiary and accepted by the Commission.

9(2) Where the amendment does not affect the basic purpose of the Operation and the financial impact is limited to a transfer within a single budget heading or a transfer between budget headings involving a variation of less than 10% of the amount originally entered under a heading for eligible costs, the Beneficiary may apply the amendment and shall inform the Commission accordingly without delay. This method may not be used to amend headings for administrative costs or the contingency reserve.

Changes of address, changes of bank account and changes of auditor may simply be notified, although this does not affect the Commission's option to oppose the Beneficiary's choice of bank account or auditor.

The Commission reserves the right to require that the auditor referred to in Article 7(1) of the Special Conditions be replaced if considerations which were unknown when the Contract was signed cast doubt on the auditor's independence or professional standards.

Article 10 – Assignment

The Contract and the payments attached to it may not be transferred or assigned to a third party in any manner whatsoever without the prior written consent of the Commission.

Article 11 - Termination of the Contract

11(1) The Beneficiary may terminate the Contract at any time by serving two months' written notice. In this event, the Beneficiary shall be entitled to payment of the grant only for the part of the Operation carried out, although this does not affect the Commission's right in cases of wrongful termination to claim full or partial repayment of sums already paid out.

11(2) In exceptional and duly justified cases, the Commission may decide to terminate the Contract by serving two months' written notice, without being required to pay compensation. In this event, the Beneficiary shall be entitled to payment of the grant only for the part of the Operation carried out.

11(3) The Commission may terminate the Contract, without giving notice and without paying compensation of any kind, where the Beneficiary:

- fails, without justification, to fulfil any of the obligations imposed and, after being given notice by letter to comply with those obligations, still fails to do so or to furnish a satisfactory explanation within 30 days of sending of the letter;
- is declared bankrupt, is wound up or is the subject of any similar proceeding;
- changes legal personality, unless an addendum acknowledging that fact is drawn up;
- fails to comply with articles 4 or 10 or falls into the situations described in Articles 1(3) or 16(6);
- makes false or incomplete statements to obtain the grant provided for in the Contract or provides reports that do not reflect reality;
- commits financial irregularities.

In that event the Commission may demand full or partial repayment of the sums already paid out under the Contract.

Prior to or instead of terminating the Contract as provided for in this Article, the Commission may suspend payments as a precautionary measure, without prior notice.

11(4) Termination of the Contract for financial irregularities shall be without prejudice to the application of other administrative measures or penalties which may be imposed in accordance with Council Regulation (EC, Euratom) No 2988/95 of 18 December 1995 on the protection of the European Communities' financial interests.

Article 12 – Duration of execution of the Operation, extension, suspension and end date

12(1) The Beneficiary must inform the Commission without delay of any circumstances likely to hamper or delay the implementation of the Operation. The Beneficiary may make a request, no later than two months before the end of the Operation's duration of execution, for the latter to be extended. The request must be accompanied by all the supporting evidence needed for it to be considered.

12(2) The Beneficiary may suspend implementation of the Operation if circumstances (chiefly *force majeure*) make it too difficult or dangerous to continue. The Beneficiary must inform the Commission without delay and provide all the necessary details. The Commission may terminate the Contract in accordance with Article 11(2). If the Contract is not terminated, the Beneficiary may resume implementation of the Operation once the conditions are right, after informing the Commission. The Operation's duration of execution is extended by an amount of time equivalent to the duration of the suspension. This is without prejudice to any amendments to the Contract which may be required to adapt the Operation to new circumstances of implementation.

12(3) The Contract shall come to an end 24 months after the end of the Operation's duration of execution, as defined in Article 2 of the Special Conditions.

The Commission notifies the Beneficiary of any postponement of the end date.

Article 13 – Applicable law and competent courts

13(1) This Contract shall be governed by Belgian law.

13(2) Any dispute between the Commission and the Beneficiary which arises from implementation of this Contract and to which no amicable settlement could be found shall be referred to the Brussels courts.

FINANCIAL PROVISIONS

Article 14 - Eligible costs

14(1) To be considered eligible in the context of the Operation, costs must:

- be necessary for carrying out the Operation, be provided for in the Contract and comply with the principles of sound financial management, in particular value for money and cost-effectiveness;
- have been incurred during the duration of execution of the Operation, as defined in Article 2 of the Special Conditions;
- have actually been incurred, be recorded in the Beneficiary's or Beneficiary's partners' accounts, be identifiable and verifiable, and be backed by originals of supporting evidence.

14(2) The following direct costs shall be eligible:

- the cost of staff assigned to the Operation, corresponding to actual salaries plus social security charges and other remuneration-related costs; salaries and costs must not exceed those normally borne by the Beneficiary, and rates must not exceed those generally accepted on the market in question;
- travel and subsistence costs for staff taking part in the Operation, provided they correspond to market rates and do not exceed the scales generally accepted by the Commission (including economy-class air fares) ;
- purchase costs for equipment (new or used) and services (transport, rent, etc.), provided they correspond to market rates;
- costs of consumables and supplies;
- expenditure on subcontracting or expenditure incurred by the Beneficiary's partners;
- costs deriving directly from the requirements of the Contract (dissemination of information, specific evaluation of the Operation, audit, translation, reproduction, insurance, targeted training for those involved in the Operation, etc.) including financial service costs (in particular the cost of transfers and financial guarantees);
- taxes, without prejudice to the terms of Article 14(4) ;
- a contingency reserve of no more than 5% of eligible direct costs, which can be used only with the prior written (by letter) authorisation of the Commission.

14(3) A fixed percentage of the Beneficiary's overheads up to a maximum of 7% of the total amount of eligible direct costs shall be eligible as indirect costs.

Indirect costs shall be eligible provided that they do not include costs assigned to another heading of the budget provided for by the Contract.

Indirect costs shall not be eligible where the Contract concerns the financing of an Operation conducted by a body which is already receiving an operating grant from the Commission.

14(4) The following costs shall not be considered eligible:

- provisions for possible future losses or debts;
- interest owed;
- purchases of land or buildings, except where necessary for the direct implementation of the Operation, in which case ownership must be transferred to the Beneficiary's local partners (where applicable) or the final recipients of the Operation once the latter has come to an end;
- currency exchange losses, without prejudice to the terms of Article 15(7);
- VAT which the Beneficiary is able to reclaim.

14(5) Any contributions in kind made by the Beneficiary and listed separately in Annex III shall not be considered eligible costs for Community financing.

The Beneficiary must, however, undertake to make such contributions in accordance with the terms of this Contract.

Article 15 – Payment and interest on late payment

15(1) Payment procedures are set out in Article 4 of the Special Conditions and follow one of the three options below:

Option 1 : Operations not exceeding 12 months' duration or involving Community financing of EUR 100 000 or less

The Commission will make grant payments to the Beneficiary in the following manner:

- an advance of 80% of the sum referred to in Article 3(2) of the Special Conditions within 60 days of receipt by the Commission of the Contract signed by both parties and, where applicable, of a financial guarantee, as defined in Article 15(4);

- the balance within 60 days of the authorising department's recording a request for payment accompanied by the final report, subject to approval of that report in accordance with Article 15(2).

Option 2 : Operations exceeding 12 months' duration and involving Community financing of over EUR 100 000

The Commission will make grant payments to the Beneficiary in the following manner:

- an advance of 80% of that part of the forecast budget for Operation's first 12 months which is being financed by the Community, within 60 days of receipt by the Commission of the Contract signed by both parties and, where applicable, of a financial guarantee, as defined in Article 15(4);

- intermediate payments of the amount indicated in Article 4 of the Special Conditions, within 60 days of the authorising department's recording a request for payment accompanied by an intermediate report, subject to approval of that report in accordance with Article 15(2);

- the balance within 60 days of the authorising department's recording a request for final payment accompanied by the final report, subject to approval of that report in accordance with Article 15(2).

Intermediate payments can be made only if the expenditure actually incurred represents at least 70% of the amount of the previous payment, as proven by the relevant intermediate report. The amount of the advance and the intermediate payments cannot exceed 90% of the sum referred to in Article 3(2) of the Special Conditions.

Option 3 : All Operations

The Beneficiary will receive the grant from the Commission as a lump sum within 60 days of the authorising department's recording a request for final payment accompanied by the final report, subject to approval of that report in accordance with Article 15(2).

Reports must be presented in accordance with the stipulations of Article 2.

15(2) The payment deadline of 60 calendar days referred to in Article 15(1) above shall expire on the date on which the Commission's account is debited. Without prejudice to the terms of Article 11(3), the Commission may halt the countdown towards this deadline by notifying the Beneficiary that the request for payment is inadmissible, either because the amount in question is not due or because the relevant report cannot be approved and the Commission thinks it necessary to conduct further checks. In such cases, the Commission may request clarification, alteration or additional information, which must be produced within 30 days of the request. The countdown towards the deadline will resume on the date on which a correctly formulated request for payment is recorded.

15(3) Once the deadline referred to above has expired, the Beneficiary (unless the Beneficiary is a government department or public body in a Community Member State) may, within two months of late payment, claim late-payment interest at the rate applied by the European Central Bank to its main refinancing transactions in euros, plus one and a half percentage points. The late-payment interest shall apply to the time which elapses between the date of the payment deadline (inclusive), and the date on which the Commission's account is debited (exclusive). This interest shall not be considered income for the purposes of Article 17(3).

15(4) Advances of EUR 1 million or more must be fully secured by a financial guarantee remaining valid until it is released by the Commission following final payment. This provision shall not apply if the Beneficiary is a government department or public body in a Community Member State.

15(5) The financial guarantee shall be in conformity with or match the model below:

SPECIMEN FINANCIAL GUARANTEE FOR THE REPAYMENT OF ADVANCES

To the Commission of the European Communities,
SCR , *[name and address of the relevant financial unit]*
200 rue de la Loi B-1049 Brussels, hereinafter referred to as "the Commission",

Subject : **Guarantee n°...**
Financial guarantee for the repayment of advances payable under grant Contract ..... ***[Contract number and title]*** **(quote number and title in all correspondence)**

We the undersigned, ... [*name and address of financial institution*] hereby irrevocably declare that we guarantee as primary obligor, and not merely as a surety, on behalf of .....[*name and address of the Beneficiary]*, hereinafter referred to as "the Beneficiary", payment to the Commission of .....[*amount of the advance in the currency in which it must be paid*], this amount representing the part of the cost of the Operation payable as an advance under grant Contract .....[*Contract number and title*] concluded between the Beneficiary and the Commission.

Payment shall be made into account .....[*account number*] held by the Commission, without objection or legal proceedings of any kind, upon receipt of your first written claim (sent by registered letter with confirmation of receipt) stating that the Beneficiary has not repaid the advance on request or that the Contract has been terminated for any reason whatsoever. We shall not delay the payment, nor shall we oppose it for any reason whatsoever. We shall inform you in writing as soon as payment has been made.

We note that the guarantee will be released 60 days at the latest after the final payment provided for in the Contract.

The law applicable to this guarantee shall be that of .....[*name of the European Union Member State in which the financial institution issuing the guarantee is established, or "Belgium" if the financial institution is established outside the European Union]*. Any dispute arising out of or in connection with this guarantee shall be referred to the Brussels courts.

This guarantee will come into force and will take effect on receipt of the advance in the account designated in the Contract by the Beneficiary to receive payments.

.....	.....
[place and date]	*[signature]*[1]

15(6) Payments due from the Commission shall be made into the bank account referred to in Article 4(3) of the Special Conditions. Where provision is made for the payment of an advance of EUR 1 million or more, a bank account must be opened specifically for the Operation.

15(7) The Commission will make payments in euros. Where necessary, actual expenditure will be converted into euros at the rate published by the European Central Bank in the "C" series of the Official Journal on the first working day of the month in which the request for payment is made. In the case of currencies not quoted in the Official Journal, conversion shall be based on the rates published in the Financial Times on the first Tuesday of the month in which the payment is made.

If there is an exceptionally wide fluctuation in exchange rates, the Commission may at the Beneficiary's request take appropriate steps to offset its effects.

15(8) Any interest accruing from the advances paid to the Beneficiary by the Commission shall be considered income for the purposes of Article 17(3). It may be used to cover eligible costs of the Operation.

Article 16 – Accounts and technical and financial checks

16(1) The Beneficiary must keep accurate and regular records and accounts of the implementation of the Operation using a dedicated double-entry book-keeping system as part of or as an adjunct to the Beneficiary's own accounts. This dedicated system shall follow the procedures dictated by professional practice. Separate accounts must be kept for each Operation, and must detail all income and expenditure. They must provide precise details of interest accruing on funds paid by the Commission.

16(2) The Beneficiary must consent to record-based or on-the-spot inspections by the Commission or the Court of Auditors of the use made of the grant, in accordance with the financial regulation applicable to the general budget of the Community (or as the case may be with the financial regulation applicable to the ACP-EC co-operation), until five years after the end date.

To that end, the Beneficiary must undertake to provide the staff of the Commission or the Court of Auditors, or their authorised agents, with appropriate rights of access to the sites and locations in which the Operation is being implemented, including access to computer systems, as well as access to all documents and computer files relating to the financial and technical management of the Operation. Access by authorised agents of the Commission or Court of Auditors shall be kept strictly confidential with regard to third parties, without prejudice to public law obligations to which the Commission is subject. Documents must be easily accessible and filed in a manner which allows easy verification; the Beneficiary is obliged to inform the Commission of the precise location in which they are kept.

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1 The name and title of the person(s) signing for the guarantor should be added in printed characters.

16(3) The documents referred to in Article 16(2) include:

A Works, supplies and services :
- bids from suppliers ;
- Contracts or order forms ;
- invoices and proofs of payment or settled invoices; if supplies come from the Beneficiary's stocks, invoices shall reflect the price paid at the time of purchase; a copy of the purchase invoice must be attached;
- for fuel and oil, the Beneficiary shall keep a summary list of the distance covered, the average consumption of the vehicles used, fuel costs and maintenance costs.

B Staffing costs :
- a statement of expenditure on expatriate and/or European-based staff (where implementation is taking place in Europe) per month of effective work; expenditure will be assessed on the basis of unit prices per verifiable block of time worked and will be broken down into gross salary, social security charges, insurance and net salary;
- a statement of expenditure on locally recruited staff on fixed-term Contracts, with details of remuneration paid in cash or kind, duly substantiated by the person in charge locally, broken down into gross salary, social security charges, insurance and net salary.

16(4) If the size of the grant is EUR 100 000 or more, a final audit will be carried out when the Operation ends. Furthermore, if the Operation's duration of execution exceeds 18 months, an annual audit will be carried out for every 12-month period of implementation after the start of the Operation.

Every audit report must cover:

- Analysis and checking of the nature, legality and regularity of expenditure ;
- Checking of the utilisation of advances ;
- Audit of third-party accounts ;
- Reconciliation of expenditure with the dedicated accounts referred to in Article 16(1) above and with the Budget for the Operation ;
- Checking of the project's income (including Community advances, interest on advances, co-financing and other income generated by the project) ;
- Information on the precise physical location of the original documentary evidence for use in the event of checks by the Commission and Court of Auditors.

The auditor will in addition perform physical spot-checks (of genuine existence and of conformity) on certain activities. The Commission Delegation responsible for supervising the Operation, or any other Commission department, will determine the activities to be spot-checked at the Beneficiary's request and before the audit takes place.

Without prejudice to the terms of Article 11(3), the audit must not interrupt the implementation of the Operation. It must be carried out in accordance with international standards in the field.

16(5) The Beneficiary may fulfil the obligations referred to in Article 16(4) by submitting either audit reports for the Operation or its own annual audit report, provided that the audit is carried out by the independent audit practice referred to in Article 7 of the Special Conditions.

16(6) If the Beneficiary fails to comply with the fundamental obligations set out in this Article 16, the Commission may terminate the Contract in accordance with Article 11(3). In addition, the Beneficiary may be ruled ineligible for further Community financing for a period determined by the Commission.

Article 17 – Final amount of Community financing

17(1) The total sum to be paid by the Commission to the Beneficiary may not exceed the maximum grant established by Article 3(2) of the Special Conditions, even if the overall actual expenditure exceeds the estimated total budget set out in Annex III.

17(2) If the eligible costs at the end of the Operation are less than the estimated total cost specified in Article 3(1) of the Special Conditions, the Community contribution shall be limited to the amount produced by multiplying the actual expenditure by the percentage laid down in Article 3(2) of the Special Conditions.

17(3) The Beneficiary accepts that the grant can under no circumstances result in a profit for the Beneficiary, and must be limited to the amount required to balance income and expenditure for the Operation.

Article 18 – Repayment of the grant

18(1) In the cases referred to in Articles 11(1) (except wrongful termination), 11(2) and 17, the Beneficiary undertakes to repay to the Commission within 60 days of receiving a request from the latter any amounts paid in excess of the final amount due.

18(2) In the event of wrongful termination of the Contract by the Beneficiary, and in the cases specified in Article 11(3), the Commission may request full or partial repayment of sums paid to the Beneficiary. The Commission shall determine the manner and the deadline for such full or partial repayment.

18(3) Should the Beneficiary fail to repay such amounts within the deadline set by the Commission, the Commission may (unless the Beneficiary is a government department or public body in a Community Member State) increase the sums due by adding interest at the rate applied by the European Central Bank on the first day of the month in which the deadline expires to its main refinancing transactions in euros, plus one and a half percentage points. The late-payment interest shall apply to the time which elapses between the date of the payment deadline set by the Commission (inclusive), and the date on which payment is actually made (exclusive).

18(4) Bank charges incurred by the repayment of sums due to the Commission shall be borne entirely by the Beneficiary.

18(5) The recovery decision drawn up by the Commission and transmitted to the Beneficiary owing a repayment to the Commission shall be enforceable within the meaning of Article 256 of the EC Treaty.

18(6) Amounts to be repaid to the Commission may be offset against amounts of any kind due to the Beneficiary. This shall not affect the parties' option to agree on payment in instalments.

ANNEX III

BUDGET FOR THE OPERATION

		Year 1	Year 2	Year 3	Total
WP1 (LANAVET)(112,2kEuros)					
T1/44-T1sr Dose effect	Labour	11			
	Animals	37	5	5	
	Transport and foo	9.2	5	5	
	Consumables	10	8.6	8.6	
	Overheads	5	1.4	1.4	
	Sub-total	72.2	20	20	112.2
WP2 (KARI)(117kEuros)					
T1/44-T1sr Boost effect	Animals	32	5	5	
	Transport and foo	27.7	5	5	
	Consumables	12	8.6	8.6	
	Overheads	5.3	1.4	1.4	
	Sub-total	77	20	20	117
WP3 (CIRAD, ILRI, KARI, LANAVET) (155kEuros)					
Search for new vaccines					
WP3.1 (ILRI)					
Evaluation of protective immunity in vaccinated catt	Consumables	37.2	27.9	27.9	
	Overheads	2.8	2.1	2.1	
	Sub-total	40	30	30	100
WP3.2 (CIRAD, Lanavet)					
Identification of virulence genes	Consumables	9.4		4.7	
	Overheads	0.6		0.3	
	Sub-total	10		5	15
WP3.3 (CIRAD)					
Identification of putative protective antigens	Consumables	23.25		13.95	
	Overheads	1.75		1.05	
	Sub-total	25		15	40
WP4 (MOREDUN CIRAD KARI) (90kEuros)					
Search for new diagnostic tests					
WP4.1 (Moredun, KARI)	Consumables	14	5	5	
Evaluation of penside test	Overheads	1			
	Sub-total	15	5	5	25
WP4.2 (CIRAD, Kari)	Consumables	27.9	18.6	13.95	
Detection of postvaccinal response	Overheads	2.1	1.4	1.05	
	Sub-total	30	20	15	65
WP5 (CIRAD) (59kEuros)	Consumables	24.5	14	16.8	
Coordination, travels and workshop	Overheads	1.5	1	1.2	
	Sub-total	26	15	18	59
AUDIT		10	10	10	30
		305.2	120	138	
				Grand total	563.2

ANNEX IV

CONTRACT AWARD PROCEDURES

ANNEX IV
CONTRACT-AWARD PROCEDURES

SERVICES	SUPPLIES	WORKS
x ≥ 200,000 € Restricted international tender. 4 to 8 service providers invited.	**x ≥ 150,000 €** Open international tender.	**x ≥ 5,000,000 €** 1. Open international tender. 2. Restricted international tender (special case).
	30,000 € ≤ x < 150,000 € Open local tender.	**300,000 € ≤ x < 5,000,000 €** Open local tender.
x < 200,000 € 1. Simplified procedure after consultation with at least 3 service providers. 2. x ≤ 5,000 € : one single offer.	**x < 30,000 €** 1. Simplified procedure after consultation with at least 3 suppliers. 2. x ≤ 5,000 € : one single offer.	**x < 300,000 €** 1. Simplified procedure after consultation with at least 3 contractors. 2. x ≤ 5,000 € : one single offer.

ANNEX V

PAYMENT REQUEST
&
FINANCIAL IDENTIFICATION FORM

ANNEX V

Request for payment for grant contract for external aid

Date of the request for payment: .....

For the attention of
The European Commission
EuropeAid Co-operation Office
C/7

Reference number of the grant Contract: **REG/5007/005**

Title of the grant Contract: **"Contagious Bovine Pleuropneumonia (CBPP)"**
PACE Research Programme

Name and address of the Beneficiary: **CIRAD-EMVT**
TA 30/B
Campus International de Baillarguet
34398 Montpellier cedex 5
FRANCE

Request for payment number: .....

Period covered by the request for payment: .....

Dear Sir/Madam,

I hereby request payment of the advance under the contract mentioned above.

The amount requested is as indicated in Article 4.2 of the Special Conditions. Please find attached the following supporting documents:
- signed contract (for payment of the advance)

The payment should be made to the following bank account: **30004 00640 00010044308 86 BNP Montpellier**

Yours faithfully,

FINANCIAL IDENTIFICATION

ACCOUNT HOLDER

NAME: CIRAD-EMVT

ADDRESS: TA 30-B
CAMPUS INTERNATIONAL DE BAILLARGUET
34398 MONTPELLIER CEDEX 5

TOWN/CITY: MONTPELLIER

POST CODE: CEDEX 5

CONTACT PERSDN: JOSEPH DOMENECH

TELEPHONE: 0033467593710

FAX: 0033467593795

VAT NUMBER:

BANK

NAME:

ADDRESS:

TOWN/CITY:

POST CODE:

ACCOUNT NUMBER:

CURRENCY: BIG CODE:

BENEFICIARY
(Only if different from account holder)

NAME:

ADDRESS:

TOWN/CITY:

POST CODE:

REMARKS : .....

DATE: ..... SIGNATURE : .....