

SCIENTIFIC DISCUSSION

1. INTRODUCTION

Ibraxion is an inactivated adjuvanted vaccine against Infectious Bovine Rhinotracheitis. The vaccine virus was obtained by deleting the genome of Bovine Herpesvirus Type 1 in the glycoprotein gE gene. The vaccine therefore possesses the gE-negative marker, which allows a differentiation between vaccinated and naturally infected cattle. The virus is inactivated with betapropiolactone. The vaccine contains glycoprotein in a light paraffin oil adjuvant. The amount of glycoprotein corresponds to a seroneutralisation antibody titre of 0.75 SN U.

The vaccine schedule consists of two subcutaneous administrations at an interval of three weeks. The minimum age for vaccination is two weeks in the absence of maternal antibodies. The revaccination is to be performed at 6 month intervals.

IBR is recognised as an important pathogen of cattle. The virus is present world-wide and causes respiratory infections with rhinotracheitis, conjunctivitis and abortion. Vaccines against IBR are used to prevent the clinical consequences of infection. They prevent neither virus excretion after primary infection or establishment of virus latency. The recent development of marker vaccines allows for differentiation between vaccinated and naturally infected animals.

The parental strain of the gE-negative Ibraxion vaccine is genetically modified by recombination. The gE gene was replaced by a truncated gene with a poly stop sequence. Data are provided that the gE-negative strain does not express gE-glycoprotein. The strain is propagated in MDBK cells.

In the safety part, the Applicant has provided evidence of safety. The data provided confirm that the vaccine has no adverse effect on reproductive performance and on milk yield when it is administered during pregnancy (early, mid-term and late pregnancy). The effect of booster vaccination of pregnant cows was also evaluated and no modification of the reproductive performance was observed.

The effect of Ibraxion on the reduction of clinical signs of IBR and the viral excretion has been well documented. Validation was presented for the vaccine scheme at 6 month intervals by assessing the effect of the booster injection with serologic study. The serologic response which can be considered as an acceptable indicator of the immunological properties of the vaccine is good even after a booster up to 15 months after the onset of vaccination.

2. OVERVIEW OF PART II OF THE DOSSIER: ANALYTICAL ASPECTS

PART II A QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

1. Composition of the veterinary medicinal product

Active substance:

Inactivated gE-deleted IBR virus 0.75 VN.Units¹

Others ingredients:

Adjuvant:

Light paraffin oil 449.6 to 488.2 mg

Excipients

q.s 2 ml

Diluent

saline solution

2. Container

Colourless type I glass of 10, 20 and 50 ml volume according to Ph.Eur. 1997 closed with nitril elastomer closures complying with the Ph.Eur. 1997, and sealed with aluminium caps.

3. Clinical trial formulations

The batch used in the laboratory trials contained an increased amount gB (glycoprotein B) /dose, corresponding to the maximum potency. For field trials, the use of lower gB per dose corresponds to the standard amount of antigen present in the vaccine. In the laboratory safety trials the vaccine contained a higher dose.

4. Product Development Studies

The manufacturer explains the choice of different development pharmaceuticals stages:

4.1 Choice of the strain:

The wild strain was isolated from a clinically infected animal. This strain has already been used in vaccines manufactured by Merial.

The modification of the strain by genetic recombination leads to a gE protein deleted virus containing vaccine enabling the differentiation between vaccinated (= free of anti-gE antibodies) and field virus infected (anti-gE antibody positive) animals. Therefore, the vaccine in question can be used as marker vaccine against Infectious Bovine Rhinotracheitis in national eradication programs. The virus is inactivated and quantified by an ELISA assay using an anti-gB monoclonal antibody acting both as a capture and a revealing antibody. The ELISA technique was validated.

The active ingredient is titrated after BPL inactivation by determination the µg content of gB protein/ml (= g/l) compared with a reference antigen using an anti-gB monoclonal antibody ELISA. The gB protein induces the synthesis of protective antibodies.

¹ 1: VN.Unit: Neutralising antibody titre of 1 log₁₀ after a single vaccination of a quarter dose in guinea pigs

4.2 Choice of the antigen concentration:

Dose-response-relationship-studies have been performed and demonstrate that vironeutralising antibodies are present to provide adequate protection. A formulation at a lower rate of gB glycoprotein per dose ensured a satisfactory protection in challenged animals. Based on the minimum protective formulation and a possible loss of potency during storage, standard formulations for the industrial batches have been chosen (that is an overage equal to 100% of the minimum protective formulation).

4.3 Choice of the adjuvant:

A classical oil in water emulsion (o/w) is used as an adjuvant which is well tolerated in cattle and already used in other Merial vaccines.

As the safety studies did not reveal any major adverse local effect, the use of light paraffin oil as adjuvant could be considered as acceptable. The light paraffin oil used complies with a Merial specification and certificates of analysis have been provided.

4.4 Preservative:

No preservative is added in the formulation.

4.5 Other excipients

Benzyl alcohol is used to stabilise the emulsion by maximising surfactant power.

Triethanolamine is used as buffer helps to minimise the acidity induced by surfactants

4.6 Filling volume:

To guarantee the minimum volume required for each bottle, an overage is added during filling.

4.7 Choice of the potency testing technique for the finished product:

The batch potency is determined after a single administration of a quarter dose to guinea pigs by measurement of neutralising antibodies. Validation data have been provided. The relation between gB content, neutralising antibodies and protection corresponds to that acceptable for inactivated vaccines. The rate and dose of administration allows the detection of a defective batch, with a dose-response relationship.

4.8 Definition of the norms:

The related release norm is 0.75 SN U. reflecting the overage in formulation.

II B DESCRIPTION OF METHOD OF PREPARATION OF THE FINISHED PRODUCT

II.B.1 Formulation

The single steps are conducted in closed and sterilised containers under conditions which comply with the Ph.Eur., or under laminar flow of grade A in a clean environment of grade B (= GMP classification).

The formulation of the vaccine is standardised by the concentration of gB glycoprotein.

Validation data of the gB glycoprotein concentration assay are submitted based on an immunocapture ELISA test using anti-gB monoclonal antibodies and including a reference preparation.

The formulation conditions for 1 ml bulk are clearly indicated. The volume of inactivated gE deleted IBR virus is influenced by the gB glycoprotein concentration. The qualitative and quantitative composition of the constituents of the adjuvant, in addition to the properties of experimental emulsions are specified by the manufacturer. The mentioned bulk constituents are sterilised according to Ph.Eur. requirements. The active ingredient undergoes a sterility testing in accordance with Ph.Eur.

The storage period of the formulated bulk before filling is limited to 2 months at +5°C.

II.B.2 Filling and blending.

Saline solution is sterilised and mixed with the active ingredient. Stirring ensures that an homogenised aqueous phase is obtained. The physico-chemical characteristics of paraffin oil, oleic oil and oleic alcohol are determined and the quantities of each necessary to obtain an appropriate emulsion are determined. These different components, together with Benzyl alcohol and Triethanolamine, are mixed and stirred.

The oily blend is then sterilised through filtration and transferred into the emulsifier. The emulsion is carried out. Bottles are sterilised by dry heat and closures are sterilised by steam (in compliance with EP 3rd edition, § 5.1.1).

The bottles are then filled, immediately closed and sealed with a cap. The secondary packaging is then carried out and the whole is stored at 5°C. The shelf life of the final product is calculated from the potency test starting date, which is performed in guinea pigs.

II.B.3. Validation studies

Results for relevant validation studies for processes applied have been provided for the following steps:

- Description of the recombinant virus
- Validation of the gE character
- Validation of the irradiation method
- Inactivation kinetics of gE deleted virus
- Validation of active ingredient inactivation control test
- Validation of active ingredient quantification control test
- Potency test validation
- Validation of serological titration control test
- Specific harvest criteria.

II C CONTROL OF STARTING MATERIALS

1 Starting materials listed in pharmacopoeia

Starting material

The following comply with the European Pharmacopoeia:

- Sodium hydrogen carbonate
- Gentamicin sulphate
- Trisaminomethane
- Sodium hydroxide
- Benzyl alcohol
- Sodium chloride
- Potassium chloride
- Potassium dihydrogen phosphate
- Disodium phosphate dihydrate
- Magnesium chloride

Calcium chloride
Water for injection
Glass container
Nitril elastomer closure

Triethanolamine complies with the French Pharmacopoeia.

Certificates of analysis performed were supplied systematically by the Applicant enclosing also copies of the monographs and therefore facilitating the comparison between the requirements of the monographs and the in-house tests at Merial.

2 Starting materials not in a pharmacopoeia

II.C.2.1. Starting materials of biological origin

The following starting materials are of biological origin and comply with a Merial monograph. Information on source and function is provided.

Starting material

1. MDBK cell line
2. Inactivated gE-deleted IBR virus
3. Crystallized trypsin
4. Foetal calf serum
5. Bovine serum
6. Lactalbumin hydrolysate

1. Madin Darby Bovine Kidney cell line (MDBK)

The Master Cell Bank (MCB) was constituted after classical production cycles. The Working Cell Bank (WCB) is established from the MCB. Production cells correspond to additional passages; the last one is carried out on microcarriers. The MCB and WCB are stored frozen in liquid nitrogen.

Control tests for the Master Cell Bank and the Working Cell Bank have been carried out including appropriate certificates of analysis and the description of adequate techniques such as:

- Origin and history
- Controls on the Master Cell Bank (MCB) and the Working Cell Bank (WCB):
 - identity and karyology.
 - viral purity by detection of cytopathogenic and haemadsorbing agents on MDBK cells and cytopathogenic and haemadsorbing agents after inoculation of a lysate of MDBK cells on cells; by specific detection - absence of bacterial and yeast contamination using a general test (Ph.Eur. test 2.6.1), specific tests
 - absence of mycoplasmic contamination (Ph.Eur. test 2.6.7).

Relevant tests on specified viruses have been carried out in accordance with the principles of the "Table of extraneous agents to be tested for in relation to the general and species specific guidelines on production and control of mammalian veterinary vaccines" (III/3427/93-EN). Titres of the positive controls used in the purity control tests have been provided. A justification based on geographical origin was provided for tests which were not carried out. However the sera used for cultivation of the MCB were tested for the absence of extraneous agents and γ -irradiated.

The general tests including identity, karyology and sterility were carried out on the cell line with satisfactory results. Tumorigenicity is not to be assumed and therefore was not tested. The propagation of cell seeds is described. It is performed in roller bottles and in a biogenerator associated to microcarriers

2. Inactivated gE-deleted IBR virus

I Genetic engineering:

In order to differentiate between infected and vaccinated animals genetic engineering was applied on IBR virus strain to delete gE gene expression.

Detailed summarising information on genetic engineering of recombinant IBR virus, including starting materials, construction of the recombinant virus, control of identity and genetic stability as well as validation of the gE character has been provided.

A Starting materials:

1. Parental IBR virus:

The initial BHV-1 strain was isolated in France 1970 from an infected bovine and belongs to the alpha herpesvirinae sub-family and the Simplex virus genus. It is an enveloped virus containing one molecule of linear double-stranded DNA of about 140 kb. Replication and transcription take place in the nucleus of the host cell. The virus underwent 7 passages in primary calf cells before construction of the gE deleted IBR virus by genetic engineering.

2. Construction of plasmids:

The genomic structure of the plasmids was provided.

B Construction of the recombinant virus:

To obtain recombinant virus, the gene of the gE glycoprotein was partially deleted from the genome

The selected clone was purified using the plaque technique in cells demonstrating the purity up to the final clone

II Recombinant IBR virus:

The obtained clone was directly used for the preparation of the Master Seed Virus (MSV) performed with passages on MDBK cells. and the Working Seed Virus (WSV) corresponds to the 4th passage from the MSV. That means a seed lot system is used for vaccine production.

The MSV and WSV are stored frozen at $\leq -70^{\circ}\text{C}$.

1. Description:

The virus is a gE-deleted recombinant virus: the gE-encoding gene of the parental IBR virus was replaced by a truncated gene containing a polystop sequence. No gene was added.

2. Control of identity and genetic stability of the recombinant virus:

2.1 Southern blot:

This demonstrates the genetic stability of the gE-deleted virus after in vitro passages.

2.2 Sequence analysis:

DNA extracted virus were digested with restriction enzymes. The 2 fragments were amplified and then sequenced. This demonstrates the genetic stability of the gE-deleted virus after in vitro passages. The comparison of the analysis sequence of the parental IBR virus strain and the recombinant virus shows the absence of any new open reading frame

The genomic charts of the parental virus (BHV ST) and recombinant virus, have been provided as well as clear photographic documentation on the results of the hybridisation of the parental and recombinant viruses with probes. The results obtained are in accordance with the expected ones confirming the gE-deleted structure.

3. Validation of the gE- character

3.1 *in vitro* study:

The presence of the IBR virus was checked by immunofluorescence, and the lack of the gE character was determined using an anti-gE monoclonal antibody. No gE expression was detected.

3.2 *in vivo* study:

Fifty bovines of various breeds, ages and physiological status received the gE-deleted IBR vaccine twice at a 21-day interval by subcutaneous route and 50 other bovines received a placebo injection under the same conditions. Blood samples were collected. The ELISA gE was negative for all the vaccinated animals.

4. Controls on the Master Seed Virus:

Controls on the Master Seed Virus included

- identity, and checking the gE deletion.
- titration
- viral purity:
 - by detection of cytopathogenic, haemadsorbing and haemagglutinating agents on various cells after having neutralized the IBR Master Seed sample
 - by specific detection
- absence of bacterial and yeast contamination:
 - by a general test (Ph. Eur. test 2.6.1).
 - by specific tests
- absence of mycoplasmic contamination (Ph. Eur. test 2.6.7).

Techniques and certificates of analysis were enclosed. All tests have been carried out according to EU requirements. With regard to the viral purity of the MSV, neutralising monoclonal antibodies have been prepared using IBR virus strain as the immunising agent. The MSV was neutralised with a pool of monoclonal antibodies from mice. A justification based on geographical origin was provided for tests which were not carried out

Controls on the Working Seed Virus:

The WSV is tested for

- identity, and checking the gE deletion.
- titration
- Sterility (absence of bacterial, mycoplasmic and yeast contamination (Ph. Eur. test 2.6.1 and 2.6.7)).

Appropriate certificates of analysis are provided for the Master Seed Virus and the Working Seed Virus.

Controls on the Active Ingredient (which corresponds to the 5th passage at most from the Master Seed Virus):

The following control tests are performed during the production stage of the active ingredient:

- Control test on inactivation
- Sterility according to Ph.Eur. test 2.6.1 (absence of bacterial and yeast contamination)
- Quantification of IBR virus glycoprotein gB using an ELISA technique. A validation test has been provided..

Certificates of analysis of three consecutively produced batches of active ingredient have been provided.

Production stages (amplification, culture, purification and inactivation) are clearly described under "Preparation and control tests" including a description of in-process controls and of validation.

Preparation of the active ingredient

Preparation of the active ingredient is conducted under a controlled environment. Culture, harvest and treatments are carried out in closed circuits in production areas. As stated above a seed lot system is used: MSV + 5 passages.

Production

After cell multiplication on micro-carriers, WSV is inoculated into the culture vessel. The virus replication is stopped by cooling to +5°C. After treatments to eliminate the micro-carriers the virus harvest suspension is heated and betapropiolactone (BPL) is added as the inactivation agent.

Inactivation

Inactivation is carried out under stirring. At the end of this period samples are taken for the inactivation test. Total inactivation is achieved within less than 67% of the inactivation process used during manufacture, which complies to the European recommendations. The gE deleted IBR virus batch of concern showed a harvest titre of 8.5 log₁₀ CCID₅₀ /ml. During a typical production campaign it is usually not intended to determine the virus titre before inactivation.

The residual BPL content was determined and the quantities of residual BPL were still detected after 16 hours but completely absent after 24 hours. Control tests on inactivation are performed on each batch by MDBK cell inoculation followed by two passages and CPE observation. The technique was validated.

The test was carried out by direct overload of infectious gE deleted IBR virus in the culture medium not taking into account the presence of inactivated particles in an inactivated virus suspension and the effects resulting thereof.

The validity of the test system itself was proven. The report validates the maximum allowed storage period at +5°C of an inactivated bulk before performing the inactivation control test.

After inactivation the viral suspension is concentrated 50 times by ultra-filtration. The concentrated and filtered viral suspension constitutes the active ingredient and is stored at -40°C. Examples of preparation of three consecutive batches are provided. Detailed information on the evaluation of tests sensitivity was also provided. The Applicant provided appropriate data to allow a shelf-life of 18 months.

1.3. Crystallised trypsin:

Crystallised Trypsin is of porcine origin and complies with the recommendations for the GRIMV. It is extracted from american pig pancreas and is gamma-irradiated. The validation of the irradiation method is provided. Before irradiation the following controls are done: characteristics; sterility (Eur. Ph. 3rd edition); extraneous agents (non specific and specific tests (pestiviruses, porcine parvovirus)) and potency test. A certificate of analysis is provided, in accordance with the monograph.

1.4 Foetal calf serum, Bovine serum, Lactalbumin hydrolysate :

A declaration has been provided that the Applicant is compliant with the requirements set out in the EU guidelines and in Commission Decision 97/534/EC.

Foetal calf serum, bovine serum and LAH, are sourced from BSE-free regions and the animals are aged less than 6 months. The substances come from USA, New Zealand, Australia, Canada and are gamma-irradiated. The validation of the irradiation method is provided.

Before irradiation the following controls are done: characteristics; sterility (Eur. Ph. 3rd edition); extraneous agents (non specific and specific tests (pestiviruses)). Certificates of analysis are provided, in accordance with the corresponding monographs.

A triple security (correct sanitary status of animals used, purity tests at arrival and gamma treatment applied) guarantees the absence of blue tongue virus in the foetal calf and bovine sera.

2.2. Starting material of non-biological origin

1. Inactivation of IBR virus:

• Betapropiolactone:

A certificate of analysis was provided, in accordance with the monograph.

2. Formulation of vaccine

• Polyoxyethylene fatty acids, Ether of fatty alcohols and polyols:

Certificates of analysis were provided, in accordance with in-house monographs.

• Light paraffin oil:

A certificate of analysis is provided, in accordance with an in house monograph

• PBS buffer:

The components are mixed and sterilized by filtration (membrane of nominal porosity $\leq 0.22 \mu\text{m}$). The following controls are done: pH, osmolality (Eur.Ph. 2.2.35) and sterility (Eur.Ph. 2.6.1). A certificate of analysis is provided in accordance with the monograph (CG/CG.EBM.98/D176).

2.3. Production medium

The culture medium for the cells is described in a monograph of the manufacturer. Media are sterilised by membrane filtration (0,22µm).

II D CONTROL TESTS CARRIED OUT AT INTERMEDIATE STAGES OF THE MANUFACTURING PROCESS

A detailed flow chart containing information on the type of tests was provided.

The tests concern the formulation (recording of sterilisation parameters - filter integrity test by bubble-point method after filtration of the adjuvant - inactivation test before blending with the oily adjuvant - recording of the temperature of the emulsion manufacturing - recording the storage temperature of the bulk), the filling (recording of the sterilisation of the bottles and closures - volume testing after filling - appearance test of the bottles after filling and closing - recording of the storage temperature) and the secondary packaging (appearance test of the labelled vials and finished product after packaging).

The test procedures were described.

II E CONTROL TESTS OF THE FINISHED PRODUCT

1. General characteristics of the finished product

Brief descriptions, codes, frequencies and functions of the tests performed, as well as limits of acceptance, have been provided by the Applicant. Appearance, volume and pH have been checked.

2. Identification and assay of the active ingredient(s)

Identity:

Identity tests were carried out to check the deletion of gE protein using a commercial diagnostic kit.

Potency:

For the release potency test, guinea pigs are administered 0.5 ml of vaccine at Day 0. Blood samples are collected for antibody titration. Antibodies are titrated by seroneutralisation. The serum titer corresponds to the inverse of the serum dilution, which neutralises 50% of the CPE caused by the virus. The mean titre obtained must be greater than or equal to release requirement.

The IBR test virus used in this test was identical to the one used in the validation test and the virus is diluted.

Validation of the titration technique

The titration technique was fully validated by a precision study using two positive sera S+ and S++ and one negative serum S- and according to the individual titres obtained. This validation allows the establishment of a control chart for the positive reference serum used on a routine basis.

The validation did not include a linearity study as it was not considered informative (the responses obtained for serial dilutions of a single positive serum are not representative of the responses obtained with different sera having different titres).

Validation of the potency test

A significant linearity between antigen concentration of 1-6-12 µg gB/ml and the antibody titre has been proven using regression analysis (linearity of $r^2 = 0,59$).

The formulation was selected for vaccine production in order to achieve a safety margin relating to a release titre of 0.75 SN Units.

3. Identification and assay of the adjuvants

Tests on density and viscosity of the adjuvants are performed according to Ph.Eur.

4. Safety tests

The safety was checked by a subcutaneous administration to 2 calves of a double dose. The animals are observed for 14 days and their rectal temperatures recorded daily from the previous day to 3 days after the injection. Measurement of the skin fold at the site of injection is performed before vaccination and at day 7 and day 14. The rectal temperature increase after vaccination must be inferior or equal to 1.5 °C with a return to normal at day 4 after vaccination. Skin fold thickness after vaccination must be inferior or equal to 30 millimeters with a return to normal at day 14 after vaccination.

5. Sterility and purity tests

The bacterial and fungal sterility complies with the Eur. Ph. 3rd edition monograph 2.6.1.. No growth must be observed.

To demonstrate that the product remains sterile over the in-use shelf-life, an experimental contamination at the end of the recommended shelf-life (6 hours after the first opening) was performed. The results obtained show that the product presents satisfactory characteristics at the end of the recommended shelf-life. Indeed, no increase of the number of microorganisms was observed 6 hours after the contamination.

6. Inactivation

Due to the presence of an oily adjuvant, the inactivation test is performed on aqueous phase during the blending of the vaccine, just before the addition of the oily phase.

7. Batch-to-batch consistency

Batch release protocols of 3 pilot batches are supplied including 1 and 5 doses sales presentations. The results were in compliance. For the three batches, density results are in accordance with the thresholds indicated in the file. As this technique is very accurate, it does not seem necessary to modify the thresholds.

II F STABILITY

Stability of the finished product

1. Shelf life

Data have been presented showing that the storage conditions can be set at +2° to +8°C, protected from light, for a duration of 18 months.

Physico-chemical characteristics, sterility, specific safety in calves and potency in guinea pigs were evaluated. All tests correspond in performance to described techniques. Sterility and safety tests were performed at T0 with satisfactory results and are to be performed at T27 months. Only a slight rise of density was observed for one batch after 6 month. But the maximum requirement was exceeded only by 0.002, which is not significant. The values at T9 and T12 month were high but within the limit.

The potency test was performed on pilot batches stored up to 15 months and 3 standard batches stored up to 12 months. The data showed no loss of potency during storage.

Another stability study was provided later with results on five batches on appearance, pH, volume, density, viscosity and potency up to 21 months. No significant variation in results over the storage period can be observed. The data support a shelf life of 18 months.

2. In-use shelf-life

To demonstrate that the product remains stable over the in-use shelf-life, physico-chemical and potency tests were performed at the end of the recommended in-use shelf-life (6 hours after the first opening). The results obtained demonstrate that the product remains satisfactory at the end of the recommended 6-hour period. Therefore a 6-hour in-use shelf-life can be accepted.

III OVERVIEW OF PART III OF THE DOSSIER: SAFETY

INTRODUCTION

The different safety studies were carried out in compliance with the requirements of Directive 81/852/EEC as amended and inactivated vaccines guidelines.

III.B. GENERAL REQUIREMENTS

All safety studies presented were conducted in the target species. In the laboratory tests, the safety was studied in calves at the recommended minimum age (15 days of age) and in pregnant cows.

In the field trials, all categories of animals for which the vaccine is intended for, i.e. calves, young bovines, pregnant and lactating cows were submitted to vaccination.

The vaccine used in the studies was manufactured in accordance with the quality requirements presented in analytical part of the dossier and originated from two batches. In laboratory trials, the batch containing an increased amount of gB/dose, corresponding to the maximum potency, was used. For field trials, the dose injected corresponds to the standard amount of antigen present in the vaccine.

The posology stated in the SPC was tested, i.e. two subcutaneous injections (2 ml) performed three weeks apart and from 15 days of age. The effect of booster vaccination was assessed by study of repeated injections.

	Type of study	Category of animals	Age	Number
Laboratory tests	One dose	calves	15 days	30
	Overdose	calves	15 days	30
	Repeated doses	calves	36 - 57 days	30
	Reproductive performance	pregnant cows	adult	20
	Reproductive performance	pregnant cows	adult	156
Field trials	in IBR-free area	calves	2-4 weeks	60
		young bulls	7-9 months	20
	in IBR-contaminated area	suckler cows	adult	40
		suckler cows	adult	40
		dairy cows	32-90 months	22

The laboratory trials were conducted in accordance with GLP principles and the field trials in accordance with GCP.

III. C. LABORATORY STUDIES

Two laboratory safety studies have been performed. One study in calves was a combined study in susceptible calves including the investigation of the safety of a single dose, a single overdose and the repeated administration of a single dose.

III. C. 3.1.1 - 3.13 Safety of the administration of a single dose, Safety of the administration of a single overdose and Safety of the repeated administration of one dose

Three groups of 10 calves, 15 days old were included in the study. All animals were seronegative for IBR antibodies at the beginning of the study. The study included the investigation of the safety of subcutaneous single dose, single overdose and the repeated subcutaneous administration of a single dose.

- Group A: a single dose (2 ml) at Day 0; slaughter at Day 15
Group B: a single overdose (4 ml) at Day 0; and
a single dose (2 ml) at Day 21 and
a single dose (2 ml) at Day 42; slaughter at Day 57
Group C: untreated animals.

The trial fulfilled the requirements of Directive 81/852/EEC as amended concerning safety of administration of one dose, of an overdose and of the repeated administration of one dose. The animals were observed at least 14 days after vaccination for local and systemic reactions. Measures of rectal temperature, bodyweight and histological examinations were performed. Only local moderate injection site reactions were observed. These reactions were transient and disappeared at the end of the study.

3.1.4 Examination of reproductive performance

The administration of a double dose and (interval 21 days) a single dose in pregnant, non-lactating cows in the third trimester of pregnancy was investigated.

A second study carried out in lactating dairy cows (early, mid-term and late pregnancy) was also provided in order to assess the influence of vaccination on milk yield.

The first study was performed in 2 groups of 10 cows in the final trimester of pregnancy. The tested animals were seronegative for IBR antibodies at the beginning of the study and received the following treatments:

- Group A: a single overdose (4 ml) at day 0 and
a single dose (2 ml) at day 21
The interval from day 0 to calving ranged from 51 to 83 days ;
Group B: untreated animals.

The trial fulfils the requirements of Directive 81/852/EEC as amended concerning examination of reproductive performance. The maximum dose and the recommended route (SC) were tested in pregnant cows. The animals were observed at least 14 days after vaccination for local and systemic reactions. Calving and clinical monitoring of the calves were studied.

No abortion was observed and the calves born of vaccinated cows were normal.

An additional study was carried out in lactating dairy cows in order to assess the influence of vaccination on milk yield. A total of a 156 Holstein dairy cows were included in the study and randomly allocated to 2 groups of 77 vaccinated and 79 control animals. The study included 30 cows in early pregnancy (day 0 – 90), 16 in mid-term pregnancy (days 90 – 180) and 2 in late pregnancy (after day 180) in the vaccinated group and 28, 15 and 7 cows in the control group, accordingly.

The vaccinated cows were administered 2 subcutaneous injections in the neck at a 21-day interval. The control cows remained unvaccinated. The trial was performed in an IBR contaminated dairy herd in Italy.

Individual milk yields were recorded 5 days before and 9 days after each injection of vaccine. One abortion was observed in a vaccinated cow 16 days after the first injection of vaccine, and without precursory symptoms. The average milk yield of the vaccinated cows was not significantly different in comparison with the control animals at each time of observation.

The two trials confirmed that the vaccine has no adverse effect on reproductive performance and on milk yield when it is administered during pregnancy (early, mid-term and late pregnancy). The effect of booster vaccination of pregnant cows was also evaluated and no modification of the reproductive performance was observed. The dose injected corresponds to the standard amount of antigen present in the vaccine and not to the maximum potency. This approach is however satisfactory insofar as it concerns field trials.

It should be noted that one cow aborted 16 days post vaccination, but this effect cannot be related to vaccination (inactivated vaccine, 16 days after administration, field trial).

III. D FIELD STUDIES

The field trials fulfil the requirements of Directive 81/852/EEC as amended concerning safety of administration of the vaccine under normal conditions. The standard dose and the recommended route (SC) were tested in different categories of animals (calves of the minimum age, young bulls, suckler cows and dairy cows) and in IBR-free or contaminated area. The animals were observed at least 14 days after vaccination for local and systemic reactions. Measures of rectal temperature, bodyweight and milking were performed.

Safety evaluation in veal calves

Two groups of 30 calves, aged between 2 and 4 weeks, were included in the study and received 2 subcutaneous vaccinations at 21-day interval with a single dose or an injection with a placebo. The animals were observed up to 36 days after vaccination for local and systemic reactions. Measures of rectal temperature and bodyweight were performed.

No significant differences between the 2 groups were observed. Following the first vaccination, 53.3% of the calves had a local reaction at the site of injection and 36.7% had a reaction after second injection. The mean size of local reaction ranged from 5.4 to 6 cm. At day 36, only 2 out of 30 animals presented a lesion consequent to first injection.

Several calves, both in the vaccinated and the control group, received respiratory treatment during the trial. However, these animals were not excluded from the trial, because the clinical signs were not linked to the vaccination (both vaccinated and control animals were affected and the vaccine is an inactivated one), and the individual treatments were not administered at time of vaccination, or close to the injection sites.

Safety evaluation in bull calves

Two groups of 10 bull calves, aged between 7 and 9 months, were included in the study, which received 2 subcutaneous vaccinations at 21-day interval with a single dose or a placebo (negative control). The animals were observed at least 14 days after the second injection for local and systemic reactions. Measures of rectal temperature, bodyweight and histological examinations were performed.

No significant differences in bodyweight and rectal temperature were observed between the 2 groups, only some animals (5 vaccinated and 2 controls) presented a transient hyperthermia. After the first injection, the skinfold thickness was significantly higher on day 2 and 3 in vaccinated animals by

comparison with controls; on day 35, no significant difference was observed. After the second injection (day 21), the skinfold thickness was significantly higher on day 22, 23, 24 and day 35 in vaccinated animals by comparison with controls. No general reaction was recorded during the monitoring period.

Safety evaluation in suckler cows in an IBR free environment

Two groups of 20 adult cows were included in the study. The animals received 2 subcutaneous vaccinations at 21-day interval with a single dose or a placebo (negative control). The tested animals were seronegative for IBR antibodies at the beginning and the end of the trial. The animals were observed at least 14 days after the last vaccination for local and systemic reactions. Measures of rectal temperature, bodyweight and histological examinations were performed. Only local moderate reactions were observed.

Safety evaluation in suckler cows in a contaminated environment

Two groups of 20 animals (39 cows and 1 bull) were included in the study. The animals received 2 subcutaneous vaccinations at 20-day interval with a single dose or a placebo (negative control). The animals were observed at least 14 days after the last vaccination for local and systemic reactions. Measures of rectal temperature, bodyweight and histological examinations were performed.

Following the first vaccination, 20 % of the animals had a local reaction and 55 % had a reaction after second injection. The mean size (length + width) of local reaction ranged from 1.6 to 7.2 cm. At day 35, only one animal presented a lesion consequent to first injection. A local reaction was observed in control animals (3 after first injection and one after second injection).

Generalised reactions were recorded in a few animals within both the vaccinated and the control group, which have not been related to the vaccination.

Safety evaluation in dairy cows in a contaminated environment

Two groups of 11 lactating dairy cows, aged between 32 and 90 months, were included in the study and received 2 subcutaneous vaccinations at 21-day interval with a single dose or a placebo (negative control). The animals were observed at least 14 days after the last vaccination for local and systemic reactions. Measurements of rectal temperature, bodyweight, milk production and histological examinations were performed.

The average milk yield between day 0 and day 35 was not statistically different between both groups. Following the first vaccination, 90.9 % of the animals had a local reaction and 81.8 % had a reaction after second injection. The mean size (length and width) of local reaction ranged from 1.7 to 5.5 cm. At day 35, 50 % of the vaccinated animals presented a small lesion consequent to first injection. A local reaction was observed in control animals (1 after first injection and 2 after second injection). No general reaction was recorded during the monitoring period.

III.C.5 Examination of immunological functions

The vaccine does not contain any substances known to induce adverse effect on the immunological functions.

III.C.6 Specific requirements for live vaccines

Not applicable.

III. E. ECOTOXICITY

The vaccine is inactivated and therefore no live organism can be excreted in the environment. The paraffin oil used as adjuvant is not considered to exert any negative impact on the environment. The risk of release of vaccine is nil as the product is parenterally administered and is not directly in contact with environment because it is manufactured in tight-closed vials. Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

Since this assessment does not indicate any potential risk for environment, no ecotoxicological studies are considered necessary.

IV. OVERVIEW OF PART IV OF THE DOSSIER: EFFICACY

A INTRODUCTION

The different efficacy studies were carried out in compliance with the requirements of Council Directive 81/852/EEC as amended and inactivated vaccines guidelines.

All efficacy studies presented were conducted in the target species and included placebo or unvaccinated animals. In the laboratory tests, the efficacy was studied in calves (15 days of age to 11 months). In the field trials, all categories of animals for which the vaccine is intended for, i.e. calves, young bovines, pregnant and lactating cows were submitted to vaccination.

The vaccine used in the studies was manufactured in accordance with the quality requirements presented in analytical part of the dossier. In one of the laboratory trials, different batches containing various amount of antigen were used in order to compare the efficacy of different formulations. For field trials, the dose, which is injected corresponds to the standard amount of antigen present in the vaccine. The recommended route of administration was used, i.e. two subcutaneous injections (2 ml) performed three weeks apart and from 15 days of age.

The efficacy of vaccination was assessed by using a well established challenge model, based on some of the recommendations of the European Pharmacopoeia for live IBR vaccines (Monograph No. 696) in 4 laboratory tests. The tests were performed in susceptible calves by inoculation of the challenge strain via intranasal route and included monitoring of typical clinical signs for IBR infection in control and vaccinated animals: fever, ocular and nasal discharge and ulceration of the nasal mucosa as well as other clinical signs (coughing, diarrhoea, prostration, anorexia). The model can be considered as a good way to reproduce the natural infection. The challenge dose retained for all the challenge studies was the one, which induced an acute and typical IBR-related clinical picture in control animals. The challenge strain used was isolated on February 1989, from the lung of a cow, issued from a local farm.

The protection 6 months after the primary vaccination (2 vaccinations, interval 3 weeks) was also assessed by challenge experiment. The efficacy was investigated in presence of passive antibodies after vaccination of calves aged 3 to 4 months.

The antibody response induced by vaccination was analysed in all the studies and showed a production of specific neutralising antibodies appearing at the latest three weeks after the first vaccination and lasting over six months.

Although a complete protection against shedding and dissemination is not achieved after vaccination with the vaccine, a significant reduction of the excretion compared to controls and thus the dissemination of the IBR virus was nevertheless demonstrated in the framework of efficacy studies.

Moreover, the vaccine efficacy was also evaluated in the worst experimental conditions i.e. vaccination in presence of maternally derived antibodies and challenge 6 months later or vaccination of latent carriers treated further with dexamethasone.

Laboratory trials

Type of study	Category of animals	Age	IBR Serologic status	Number of animals
Dose titration	calves	1 month	seronegative	29
Duration of immunity	calves	2 weeks	seronegative	14
	calves	3-4 months	seropositive	12
Dexamethasone treatment	calves	10-11 months	seropositive	12

Field trials

Type of study	Category of animals	Age	IBR Serologic status	Number
IBR free environment	calves	2-4 weeks	seronegative	60
	calves	3 months	seronegative	9
	young bulls	7-9 months	seronegative	20
	suckler cows	adult	seronegative	40
IBR contaminated environment	suckler cows	adult	seropositive	40
	suckler cows	adult	seropositive	97
	dairy cows	32-90 months	seropositive	22

The laboratory trials were conducted in accordance with GLP principles and the field trials in accordance with GCP.

IV. A LABORATORY TRIALS

4.1 Dose-titration study in one-month old susceptible calves by challenge

Seven groups (n=2-5) of 29 one-month old calves, free from antibodies against IBR, were included in the study. The calves received 2 subcutaneous vaccinations at 21-day interval with a single dose (2 ml) of various gB content per dose, a positive control preparation (commercial vaccine) or a placebo (Phosphate Buffer Saline). The recommended route and the recommended posology were tested.

The animals were challenged 14 days after vaccination by using a well established IBR challenge model, with each animal receiving 5 ml of viral suspension by nasal instillation.

The calves were observed for 14 days after the challenge for local and systemic reactions, IBR-related symptoms, rectal temperature and bodyweight. The serologic response was monitored during the study using a Vironneutralising method. Necropsy was performed on all calves vaccinated with some of tested vaccines or the positive control on day 49.

After challenge, a significant reduction of clinical scores of IBR-related symptoms, temperature and virus isolation was observed for vaccinated animals. The control group showed a higher average virus titre between day 2 and day 10 post-challenge. Seroconversion was noted as early as day 21 in all the vaccinated groups. Necropsy revealed no lesions at the injection sites and only poor specific IBR virus infection lesions, such as presence of mucous secretions in the trachea of 2 animals. No lesions of the nasal mucosa were recorded.

4.1.2 Duration of immunity:

Two tests were performed in order to evaluate the duration of immunity in absence and in presence of maternally derived antibodies. Both studies comply with the requirements of Directive 81/852/EEC as amended concerning efficacy. The standard formulation, the recommended route and the recommended posology were tested in calves 2 to 6 weeks old. The animals were challenged several months after the primary vaccination.

The performance of the vaccine in these trials was lower than in the dose titration study but a significant reduction of clinical score and virus isolation was observed for vaccinated animals. In the second trial, the protection was not as good as in the trial using calves devoid of specific maternal antibodies. This is taken into account in the SPC by specifying that the vaccine must be administered to calves not less than 3 to 4 months of age in the presence of specific maternal immunity.

Duration of immunity challenge study in absence of maternally derived antibodies

Thirteen two-week old calves, free from antibodies against IBR, were included in the study and received 2 subcutaneous vaccinations at 21-day interval with a single dose or remained unvaccinated (negative control).

The animals were challenged about 6 months (day 218) after vaccination by using a well established IBR challenge model, with each animal receiving 5 ml of viral suspension by nasal instillation.

The calves were observed for 15 days after the challenge for local and systemic reactions, IBR-related symptoms, rectal temperature and bodyweight. The serologic response was monitored during the study using an ELISA for screening at arrival, a seroneutralisation and an ELISA to detect anti-gE antibodies at day 35 and 218.

After challenge, a significant reduction of clinical scores of IBR-related symptoms, temperature and virus isolation was observed for vaccinated animals. The control group showed a higher average virus titre between day 2 and day 10 post-challenge. The viro-neutralising antibody titers were significantly higher in the vaccinated group from day 21 to day 232. All the animals were gE seronegative at day 35 and day 218. Although complete protection against shedding and dissemination is not achieved after vaccination, the virus shedding was significantly lower in the vaccinated group at day 4, 6, 7, 8, 9, 10 and 12 after challenge.

Duration of immunity challenge study in presence of maternally derived antibodies

Twelve calves, 4 to 6 weeks old and presenting antibodies against IBR, were included in the study and received either 2 subcutaneous vaccinations at 21-day interval with a single dose or remained unvaccinated (negative control). The animals were challenged about 9 months (day 280) after vaccination by using a well established IBR challenge model, with each animal receiving 5 ml of viral suspension by nasal instillation.

The calves were observed for 14 days after the challenge for local and systemic reactions, IBR-related symptoms, rectal temperature and bodyweight. The serologic response was monitored during the study using an ELISA for screening at arrival, a sero-neutralisation test and an ELISA to detect anti-gE antibodies at day 35 and 218. After challenge, a significant reduction of clinical scores of IBR-related symptoms, temperature and virus isolation was observed for vaccinated animals. The control group showed a higher average virus titre between day 2 and day 10 post-challenge. The viro-neutralising antibody titers were significantly higher in the vaccinated group during the study. The increase of antibodies was higher in the vaccinated group fourteen days post-challenge. All the animals were gE seronegative the day of the challenge. Although complete protection against shedding and dissemination is not achieved after vaccination, the virus shedding was significantly lower in the vaccinated group from day 0 to 14 after challenge.

4.1.3 Virus excretion in immuno-depressed animals:

Efficacy study in IBR infected calves treated with dexamethasone

Twelve calves, 10 to 11 months old, previously challenged with the IBR virus on day 0 using a well established IBR challenge model, with each animal receiving 5 ml of viral suspension by nasal instillation, were included in the study. The calves received either the recommended route and the recommended posology of 2 subcutaneous vaccinations with a single dose on day 63 and day 84, or remained unvaccinated (negative control).

All animals received injections with 0.1 mg dexamethasone/kg bw per day during 5 consecutive days between day 98 and day 102 in order to induce virus re-excretion. The calves were observed for 29 days after the last vaccination for local and systemic reactions, IBR-related symptoms, rectal temperature and bodyweight in vaccinated animals and untreated animals. Virus isolation and the serologic response were monitored at days 15, 35, 49, 84 and from 98 – 113.

The vaccination of persistently infected animals submitted to dexamethasone treatment allows a limitation of re-excretion of the virus. After challenge, a significant reduction of clinical scores of IBR-related symptoms was observed for vaccinated animals. The Vironeutralising antibody titers were significantly higher in the vaccinated group at day 84 and day 98.

Although complete protection against shedding and dissemination is not achieved after vaccination, the virus shedding was significantly lower in the vaccinated group from day 103 to 106 after challenge.

4.2 FIELD TRIALS

Field trials have been performed in IBR free (n=4) and IBR contaminated (n=3) herds in animals of different categories and age groups. In these trials, the standard formulation, the recommended route and the recommended posology were tested. The effect of a booster injection at 15 months after the primary vaccination was studied in 2 trials. The efficacy of vaccination was assessed by monitoring the serologic response in IBR free and contaminated environment. The detection of anti-gE antibodies was performed at the end of each study.

The vaccine induced a significant and specific sero-neutralising antibody response.

4.2.1 Field trials in IBR free environment

Efficacy in veal calves

Two groups of 30 calves, aged between 2 and 4 weeks, were included in the study and received either 2 subcutaneous vaccinations at 21-day interval with a single dose or an injection of a placebo. The serologic examinations included total antibody titration by ELISA and seroneutralisation for animals testing positive on day 0; seroneutralisation on day 21 and detection of anti gE antibodies by seroneutralisation and ELISA on day 36. The mean viro-neutralising antibody titres were significantly higher in the vaccinated group than in the control group at day 21 and 36.

Efficacy in bull calves

Two groups of 10 bull calves, aged between 7 and 9 months, were included in the study and received either 2 subcutaneous vaccinations at 21-day interval with a single dose or an injection of a placebo. Serologic examinations included seroneutralisation on days 0, 21, 35 and 165 and anti gE antibody detection by ELISA on days 165. At day 0, all animals were seronegative. The control group remained negative during the study. The vaccinated animals presented a seroconversion with a peak on day 35. All animals were gE negative on day 165.

Efficacy in suckler cows

Two groups of 20 cows, aged between 7 and 9 months, were included in the study and received 2 subcutaneous vaccinations at 21-day interval with a single dose or an injection of a placebo (negative control). Serologic examinations included total antibody titration by ELISA and seroneutralisation for animals testing positive on day 0, seroneutralisation at day 21 and anti gE antibody detection by seroneutralisation and ELISA at day 35. The vaccinated animals presented a seroconversion with a peak in viro-neutralising antibody titre on day 35. All animals were gE negative on day 35.

Efficacy of a booster vaccination

Eight calves, aged between 3.5 and 4 months old, received 3 subcutaneous vaccinations with a single dose on day 0, 21 and 196 (e.g. 6 months after the primary vaccination), another calve remained untreated (negative control). Serologic examinations included the total antibody titration by seroneutralisation on day 0, 21, 36, 56, 84, 112, 140, 168, 196 and 210 and anti gE antibody detection by ELISA on day 210.

At day 0, all animals were seronegative. The control animal remained negative during the study. The vaccinated calves presented a seroconversion with a peak on day 36 and another peak on day 210. All animals were gE negative on day 210. The effect of a booster injection was studied using the serologic response (SN) after vaccination. This can be considered as an acceptable indicator of the immunological properties of the vaccine. However, the number of animals used was considered as being too small. Therefore, another study was provided later, including 12 animals from the previous study in suckling cows and 12 untreated control animals. The 12 vaccinated cows received a booster injection subcutaneously at day 476 (i.e. about 15 months after the primary vaccination). The serologic response provided by these tests confirmed the effect of a booster injection at 15 months after the primary vaccination. Thus, the vaccination scheme presented in the SPC which requires a booster injection at 6 month intervals was fully validated.

4.2.2 Field trials in IBR contaminated environment

Efficacy in suckler cows

Two groups of 20 cows were included in the study. The animals received either 2 subcutaneous vaccinations at 20-day interval with a single dose or an injection of a placebo. Serologic examinations included total antibody titration by ELISA and seroneutralisation for animals testing positive at day 0, sero-neutralisation at day 21 and anti-gE antibody detection by seroneutralisation and ELISA at day 35. At day 0, 32 out of 40 animals had a positive ELISA result (17 vaccinated and 15 controls) and no significant difference was observed between the groups. The mean viro-neutralising antibody titres were significantly higher in the vaccinated group than in the control group at day 21 and 35.

In a further study, 97 adult suckler cows were included in the study. 48 animals received 2 subcutaneous vaccinations at 21-day interval with a single dose and 49 animals received injections of a placebo according to the same scheme. Serologic examinations included total antibody titration by ELISA and seroneutralisation for animals testing positive at day 0, seroneutralisation at day 21 and anti-gE antibody detection by seroneutralisation and ELISA at day 35. At day 0, 35 out of 97 animals had a positive ELISA result (19 vaccinated and 16 controls) and no significant difference was observed between the groups. The mean vironeutralising antibody titres were significantly higher in the vaccinated group than in the control group at day 21 and 35. At day 35, 17 vaccinated and 14 control cows had a positive IBR ELISA gE result.

Efficacy in dairy cows

Two groups of 11 lactating dairy cows, aged between 32 and 90 months, were included in the study and received either 2 subcutaneous vaccinations at 21-day interval with a single dose or an injection of a placebo (negative control). Serologic examinations included total antibody titration by ELISA and seroneutralisation for animals testing positive at day 0, seroneutralisation at day 21 and anti-gE antibody detection by seroneutralisation and ELISA at day 35. At day 0, 5 out of 22 animals had a negative or borderline ELISA result and no significant difference of the average antibody titre was observed between the groups. The average sero-neutralising antibody titres were significantly higher in the vaccinated group than in the control group at day 21 and 35. Between day 0 and day 35, the average sero-neutralising antibody titres of the control animals remained constant.

RISK-BENEFIT ASSESSMENT AND CONCLUSION

Ibraxion is a gene specific deleted (gE), inactivated and adjuvanted (o/w emulsion) vaccine which acts by the active immunisation of cattle characterised by the production of Infectious Bovine Rhinotracheitis (IBR) viro-neutralising antibodies. The Applicant has provided sufficient data to demonstrate that the method of production and inactivation have been appropriately controlled. Both the shelf-life and the in-use shelf-life (15 months and 6 hours respectively) have been justified.

The data provided indicate that the vaccine is safe in the target species. Safety of the product has been studied according to the posology and method of administration which are mentioned in the SPC. Adequate information has been given in part 5.3. of the SPC on the undesirable effects that can be observed after vaccination (transient tissue reaction at the site of injection, which may persist for some weeks; vaccination may cause a slight rise in body temperature (less than 1°C) for a transient period (less than 48 hours after injection); the rare possibility of a hypersensitivity reaction). The use during pregnancy and lactation showed no side effects other than those mentioned in the section «Undesirable effects». Whilst local injection site reactions were seen after vaccination and considered as being due to the light paraffin adjuvant, these reactions considered to be sufficiently mild and outweighed by the benefits produced in immunising cattle against IBR.

The effect of Ibraxion in the reduction of clinical signs of IBR and the viral excretion has been sufficiently documented.

In efficacy trials, the standard formulation, the recommended route and the recommended posology were tested in all categories and age groups of animals. From the data available in the efficacy part, it can be concluded that a useful effect of vaccination was observed. The protection was demonstrated by a significant reduction of the clinical score and the virus excretion after challenge. The effect of maternally derived antibodies was investigated and it was shown that the vaccine must be administered to calves not less than 3 to 4 months of age in the presence of specific maternal immunity. This point is clearly indicated in the SPC.

The results of the trials showed that a duration of protection of six months is induced by the primary vaccination. Furthermore, studies have been provided, which confirmed the effect of a booster injection at 15 months after the primary vaccination. Thus, a validation was provided for the recommended vaccination scheme, which requires a booster injection at 6 month intervals by assessing the effect of the booster injection with serologic study. The serologic response, which can be considered as an acceptable indicator of the immunological properties of the vaccine, is fully acceptable even after a booster up to 15 months after the onset of vaccination.

Based on the original and complementary data presented, the Committee for Veterinary Medicinal Products concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Council Directive 81/852/EEC, as amended, and supported the claim for the active immunisation of cattle to reduce the clinical signs of infectious bovine rhinotracheitis (IBR) and field virus excretion.
