SCIENTIFIC DISCUSSION

Invented Name:	Purevax RC
Active substance / INN:	Attenuated feline rhinotracheitis herpesvirus (FVH F2 strain): at least 4.9 log 10 CCID50 per dose Inactivated feline calicivirosis antigens (FCV 431 and FCV G1 strains): at least 2.0 ELISA U per doses
Target species:	Cats
Therapeutic indication:	Active immunisation of cats of 8 weeks of age and older: - against feline infectious rhinotracheitis to reduce clinical signs, - against calicivirus infection to reduce clinical signs and excretion. -
Withdrawal period:	Not applicable
Pharmaceutical form:	Lyophilisate and solvent for suspension for injection
ATCvet code	QI
Pharmaco-Therapeutic Group	Immunologicals
Marketing Authorisation Holder	Merial 29 avenue Tony Garnier 69007 LYON France

1. SUMMARY OF THE DOSSIER

Purevax RC is a non-adjuvanted vaccine against feline viral rhinotracheitis (modified live feline herpesvirus F2 strain) and calicivirosis (combination of two inactivated purified viruses, FCV431 and FCVG1 strains).

The vaccine consists of a lyophilisate containing the active ingredients of feline viral rhinotracheitis and calicivirosis.
The claims of the vaccine are:

Active immunisation of cats of 8 weeks of age and older:
- against feline infectious rhinotracheitis to reduce clinical signs,
- against calicivirus infection to reduce clinical signs and excretion,

The vaccination schedule recommends the subcutaneous injection of a first dose of 1 ml of vaccine from the age of 8 weeks. Three to 4 weeks later, a second dose of 1 ml of vaccine is injected. Annual booster vaccination is recommended for all components.

2. QUALITY ASSESSMENT

Composition

Active substances:
Per 1 ml dose:
Freeze-dried pellet:
Attenuated feline rhinotracheitis herpesvirus (FHV F2 strain) ..... $\geq 10^{4.9}$ $CCID_{50}$[1]
Inactivated feline calicivirosis antigens (FCV 431 and G1 strains) ..... ≥ 2.0 ELISA U.
Excipient:
Gentamicin ..... at most 34 µg
Solvent:
Water for injections..... q.s. 1 ml

[1]: cell culture infective dose 50%

Container

Bottle (freeze-dried pellet or solvent) closed with an elastomer-derived closure and sealed with an aluminium cap.

Development Pharmaceutics

The development of Purevax RC addressed the 3 major features of the vaccine. These are the absence of an adjuvant, the inclusion of a new calicivirus antigen as well as the fact that Purevax RC is one of the products of a complete line with several combinations allowing veterinarians to adapt the vaccination programme to the needs of the cats depending on their environment and way of life. This is an efficient way to increase flexibility of use and to avoid over-vaccination. This contributes to a better safety of vaccination in the feline species.

The choice of both the vaccine strains and the antigen quantification method was adequately demonstrated. The formulation was demonstrated to be the best suited pharmaceutical form for a live virus

vaccine. The overage, release specifications and formulation targets were satisfactory for this type of vaccine.

Method of manufacture

The different stages of production (formulation, filling, freeze-drying and packaging) were described in a detailed manner. All the operations are carried out in closed circuit, except for the transfer into the vessels of the active ingredients thawed in a waterbath initially set at 37°C (± 3°C) which is carried out under laminar air flow hood (grade A) in clean, contained production areas of grade B (Good Manufacturing Practice (GMP) classification). All connections are sterilised by steam or gamma-radiated. When sterilisation operations are described, these are carried out in compliance with the current edition of the European Pharmacopoeia.

CONTROL OF STARTING MATERIALS

Active substance

The active ingredients used in the production of the veterinary vaccine, the attenuated feline herpesvirus, the inactivated feline calicivirus 431 antigen and the inactivated feline calicivirus G1 antigenwere adequately characterised, their origin detailed and the processing explained.

Excipients

The substances of biological origin used in the production of the veterinary vaccine, lactalbumin hydrolysate, calf serum, trypsin, foetal calf serum, Pronase, casein hydrolysate, collagen hydrolysate and tryptase phosphate broth (TPB) were adequately characterised, their origin detailed and the processing explained and compliance with the relevant Ph. Eur.monographs demonstrated.

All starting materials of non-biological origin were listed and satisfactory certificates of analysis provided.

Qualitative and quantitative compositions of all media were provided. The media, after undergoing a prefiltration step, were sterilised by filtration through a membrane of nominal pore size ≤ 0.22 µm. Filter integrity tests are carried out.

Packaging

All packaging material was of a satisfactory nature.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

This vaccine is intended for cats. Cats and other felidae have been shown to be susceptible to TSE when exposed to infectivity by the oral route. However, as cats are domestic animals there is no discernable risk of spreading the disease.

Lactose monohydrate, Lactalbumine hydrolysate and Casein hydrolysate
The milk derivatives are considered to be in compliance with the NfG provided that the milk is sourced from healthy animals in the same conditions as the milk collected for human consumption and that the calf rennet, if used during the preparation of the lactose, complies with the public statement on lactose prepared using calf rennet of the EMEA/CPMP/571/02.

Tryptose Phosphate Broth
The milk used in tryptose phosphate broth is sourced from healthy animals and the applicant confirmed that the milk is fit for human consumption and that no rennet is used.

F10-199 medium
The F10 medium does not contain any component of animal origin. The 199 medium contains cholesterol from New Zealand sheep wool and does not contain any other material of animal origin. No cases of scrapie have been reported in New Zealand. It is considered by the "Note for Guidance on minimizing the risk of transmitting TSE agents via human or veterinary medicinal products" that wool derivatives are in compliance with this Note for Guidance provided the wool is sourced from live animals.

Calf serum, Foetal calf serum
Copies of EDQM certificates were provided for all mentioned suppliers except one, for which a scientific dossier was provided.

Collagen hyrolysate
A copy of the EDQM certificate has been provided.

CrFK cells (Crandell Feline Kidney cell line)
MDCK cells (Canine kidney cell line: Madin-Darby Kidney Cell Line)
IRC5 cells (Cat kidney line cells Iffa Rein de Chat 5)
Attenuated Feline herpesvirus
Inactivated Feline calicivirus 431 antigens
Inactivated Feline calicivirus G1

The origin of all these cell lines and viruses was described in satisfactory detail and any safety issues relating to the potential TSE risk were adequately addressed.

The starting materials of animal origin used in the production of the final product comply with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.2) and Directive 2001/82/EC.

Control tests during production

The specific tests carried out during the production of the active ingredients were described.
The other tests concerned formulation, filling and packaging. They included

- time recording
- temperature recording
- viral purity
- monitoring of the sterilisation cycle (compliant with Ph.Eur., 5.1.1),
- checking of the filled volume,
- checking of the freeze-drying cycle,
- checking of the appearance of the product after capping,
- checking of the appearance of the product after labelling,
- checking of the appearance of the product presentation after packaging,
- checking the filter integrity in compliance with Ph. Eur. 5.1.1.

and while no certificate exists for these tests, they will be present in the batch record.

CONTROL TESTS ON THE FINISHED PRODUCT

General tests included the appearance and the pH of the lyophilisate and the solvent, as well as the volume and the compatibility of the solvent.

Stability of the finished product

Lyophilisate
The study was carried out on three batches of RC freeze-dried pellet. Results show the stability of the vaccine after a storage period of at least 21 months at 5°C ± 3°C in bottles protected from light. The physico-chemical parameters (pH, residual humidity) remain stable during the 21 months storage period. The bacterial, fungal and mycoplasmic sterility, as well as the safety is demonstrated after 27 months of storage. Titrations are carried out at different times during the storage period. The titres of each valence remain within the specification after 21 months of storage. The average loss of titre can be estimated after 21 months of storage to be - 0.30 log10 CCID50 for the FHV component, - 0.10 ELISA units for the FCV component. Based on the results obtained, an 18-month shelf life is justified at 5°C ± 3°C in bottles protected from light.

Solvent
The stability study of the solvent was carried out on three batches of aqueous solvent containing water for injections, stored for 39 months at 5°C ± 3°C in bottles protected from light.

The physico-chemical parameters remain unchanged during the storage period.

The bacterial and fungal sterility test is only performed once, on T0.

Consequently, a shelf-life of 36 months at 5°C ± 3°C in bottles protected from light is justified for the solvent.
A stability study was carried out on the reconstituted vaccine stored at 22°C for 2 hours. This study was carried out on three batches. On the one hand, it was intended to evaluate the stability of the reconstituted vaccine during 2 hours at 22°C ±3°C, on the other hand, it is also intended to evaluate the possible virucidal activity of the solvent on the components of the freeze-dried pellet: FHV and FCV.

The general conclusions were:

- The stability of the reconstituted product is very good for FHVand FCV and the vaccine can be kept for 2 hours after reconstitution at + 22°C ± 3°C, protected from light.
- There is no significant time effect (2 hours) on the vaccine potency when water for injections is used as a solvent.

OVERALL CONCLUSION ON QUALITY

The analytical part is generally well documented. The production and control of starting materials follows the recommendations of the EU note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01-Rev.1).

The Applicant nevertheless provided the following commitments relating to Part 2 of the dossier.

1) As the CVMP decided that the sizes of the batches used in the validation study were not adequate for the proposed production of up to 200000 vials of lyophilisate the Applicant committed to limit the production to 80 000 vials. In the case that the Applicant intends to scale up its production from 80 000 to 200 000 vials the Applicant will apply for a variation.
2) The Applicant committed to placing the first two manufacturing scale batches into a long-term stability programme after the granting of the Marketing Authorisation.
3) The Applicant committed to use gentamicin sulphate, lactose monohydrate, sodium chloride and sorbitol which comply with the new Ph. Eur. monographs.
4) The Applicant committed to send all the final experiment reports corresponding to the stability studies of the active ingredients as soon as they are finalised.

3. SAFETY ASSESSMENT

A major feature of Purevax RCis the absence of adjuvant. Tolerance at the injection site is of great importance in feline vaccinology. It was, therefore, decided to develop an adjuvant-free vaccine so as to limit the inflammatory reaction at the injection site. As a consequence of the absence of adjuvant, the feline viral rhinotracheitis of the vaccine is a modified live agent), with the feline calicivirus component, which has been inactivated.

Importantly, Purevax RC contains 2 components which have already been registered and widely used in North America (feline viral rhinotracheitis component). The only new component is the inactivated calicivirus antigen combination.

The safety studies have not been carried out using the vaccine under application Purevax RC but using the vaccine Purevax RCPCh FeLV. This vaccine contains the same components as Purevax RC and three additional components, a modified live parvovirus against infectious panleucopenia, a modified live *Chlamydophila felis* against feline chlamydiosis and a recombinant FeLVcanarypoxvirus against feline leukaemia.

This safety approach is acceptable and in line with the Note for Guidance CVMP/IWP/52/97-FINAL "Requirements for combined veterinary vaccines", as stated in section 3. Safety Aspects: "safety tests carried out on the combined vaccines may be regarded as sufficient to demonstrate the safety of the individual components or vaccines containing a smaller number of components providing the components (antigens, composition of excipients and/or adjuvants) are identical in each case and it is only the number of active ingredients which is changed".

Consequently all references to studies indicated in the safety assessment will refer to Purevax RCPCh FeLV and references to the Panleucopenia, Chlamydia and Leukaemia component will only be deleted were appropriate.

The safety trials were carried out in the target species i.e. cats, in both young and adult animals.

The vaccine dose administered to the cats corresponded to that recommended in the instructions for use.

The batches of vaccines used in the trials were produced in accordance with the manufacturing process, described in the analytical dossier.

For some trials, vaccines containing the same vaccine strains as Purevax RC, but not systematically all together, were used. These vaccines are called: Feliniffa™ (P component), Eurifel FeLV (FeLV component) and Eurifel RCChPFeLV (HCChP and FeLV components). Vaccines containing equivalent components, but from vaccine strains different than those present in the Purevax RCPCh FeLVvaccine have been used in some trials in order to allow comparisons with the Purevax RCPCh FeLV vaccine: Competitor Product A (FeLV component) and Competitor Product B (HCChP components).

Purevax RC is an associated vaccine containing live and inactivated components: a modified live feline herpesvirus (F2 strain) and a combination of two inactivated purified caliciviruses (FCV431 and FCVG1 strains). The vaccine does not contain any adjuvant.

No study on the safety of the administration of one dose was specifically conducted. The Applicant referred to a combined study on the safety of the administration of an overdose followed by two repeated administrations of one dose.

Concerning the repeated administration of one dose, the titre administered for the C component was below the maximum release titre but these deviations were satisfactorily justified.

The results of the overdose shows transient hyperthermia occurring 4 hours after the injection and lasting from 24 to 48 hours, exceptionally 5 days. Hyperthermia was still observed after 72 hours in 50% of the animals. No other systemic reactions were observed. Local reactions at the injection site were transient pain and swelling. A significant but transient decrease in the number of circulating leukocytes was frequently observed.

Following the repeated administration of one dose, transient hyperthermia was rarely observed. Local reactions were transient pain and swelling. Repeated injections do not amplify the adverse effects already observed following the administration of an overdose. A significant but transient decrease in the number of circulating leukocytes was frequently observed after the second injection.

A study was carried out to evaluate local safety of the Purevax RC vaccine by histology of the injection site. In all injection samples, only minimal to moderate reactions could be observed. On two occasions, no reaction could be detected on histological examination. In conclusion, the local safety of the non-adjuvanted combined Purevax vaccine, administered by subcutaneous route was good and the reactions at injection site were mild to moderate. No specific study has been carried out to evaluate the impact on reproductive performance. The SPC adequately recommends not to vaccinate pregnant animals.

The feline herpesvirus F2 strain seems not to disseminate in cats. However the absence of spreading has not been confirmed. Given the narrow host range susceptibility to FHV-1, no safety concern to species other than felidae is expected. Due to the high genetic stability of FHV and to the absence of spread of the vaccine virus, the risk of recombination between the FHV F2 strain and any wild type strain or different vaccine strains would be negligible.

Two field trials were conducted including 115 cats of different age and breed. They were carried out with the Purevax RC vaccine at maximum potency or at potency close to maximum for all the components.

The general reactions observed were apathy and/or anorexia, rarely hyperthermia. In most cases they were transient (less than two days). It should be noted that lethargy and apathy observed in the field were not recorded in laboratory trials. These reactions are, however, not unexpected and were therefore mentioned in the SPC. The local reactions were pain at injection site and swelling, as already observed in laboratory trials.

A main deficiency in the field trials was that no kittens of the minimal recommended age of 8 weeks have been vaccinated. The Applicant, therefore, performed a new field study including kittens and cats ranging from 6.4 weeks to 16.3 years. A significant number of kittens (n = 78) aged 1.5 – 3 months were included. The vaccine used was a commercial formulation containing the vaccinal valences at intermediate potency. No other reactions were seen as in the laboratory studies and the previous field studies, except for a slight shock reaction in one cat. This study confirmed the safety of the vaccine under field conditions.

No potential risk for the environment is expected.

4. EFFICACY ASSESSMENT

Purevax RC is a non-adjuvanted vaccine against feline viral rhinotracheitis (modified live feline herpesvirus F2 strain), and calicivirosis (combination of two inactivated purified viruses, FCV431 and FCVG1 strains) .

The Purevax vaccines have been developed to offer a non-adjuvanted vaccine range affording a satisfactory protection after a classical primary vaccination with two administrations and one annual booster (less if feasible). This has primarily driven the choice towards live components (except for calicivirus).

The valences of the vaccine are those recommended for the primary vaccination of kittens. FHV-1 is responsible for feline viral rhinotracheitis, a respiratory and ocular disease; FCV is responsible for acute and chronic gingivo-stomatitis. Both agents are commonly associated in a syndrome called "feline coryza", occurring at a high incidence in all cat populations. The composition of the vaccine is, therefore, most relevant with regard to these high incidence viral pathologies in the cat.

The efficacy studies have not been carried out using the vaccine under application Purevax RC but using the vaccine Purevax RCPCh FeLV. This vaccine contains the same components as Purevax RC and three additional components, a modified live parvovirus against infectious panleucopenia, a modified live *Chlamydophila felis* against feline chlamydiosis and a recombinant FeLV canarypoxvirus against feline leukaemia.

This efficacy approach is in line with the Note for Guidance CVMP/IWP/52/97-FINAL "Requirements for combined veterinary vaccines", as stated in section 4. Efficacy Aspects: "test results from large combinations should be acceptable for smaller combinations of the same antigens … providing the components (antigens, composition of excipients and/or adjuvants) are identical in each case and it is only the number of active ingredients which is changed". The presence of additional components is very unlikely to induce synergistic interactions as it is not antigenically related to one of the other components.

Consequently all references to studies indicated in the efficacy assessment will refer to Purevax RCPCh FeLV and references to the Panleucopenia, Chlamydia and feline leukaemia component will only be deleted were appropriate.

The trials have been conducted both in the laboratory and in the field, using the recommended route of administration (subcutaneous).

The tests were carried out in accordance with the requirements in force at the time of their implementation and enabled the evaluation of the efficacy of Purevax RC under the proposed conditions of use.
The requirements of Directive 2001/82/EC concerning efficacy trials in live and inactivated vaccines were met. For feline viral rhinotracheitis and calicivirus components, the efficacy was demonstrated in accordance with Eur. Ph. monographs No.1206 and 1101 respectively.

The choice of the vaccinal strains was considered appropriate.

All the efficacy trials were carried out in the feline species, in young and adult animals. The dose used in the efficacy trials had a volume of 1 ml (claimed quantity for a dose of this product). Vaccines were administered via the recommended subcutaneous route of administration, according to the schedule of vaccination.

The efficacy of the vaccine in conventional kittens (as opposed to SPF kittens) of the minimal recommended age for vaccination has not been investigated considering the difficulties to perform adequate serological and challenge studies in young conventional kittens. This can be considered as

justified regarding the data provided on the kinetics of maternally derived antibodies (MDAs). Indeed for kittens the difference between SPF animals and conventional ones is the presence of MDAs. The Applicant provided data showing that for most components the MDA had disappeared and/or decreased to very low level for FHV and FCV.

Protection against feline infectious rhinotracheitis

The determination of the minimal protective dose for the herpesvirus component was supported by two studies. Firstly, a study showed that the FHV F2 strain administered at a titre of at least 5.5 $\log_{10}$ $CCID_{50}$ in 10-week-old cats reduces clinical signs and viral excretion against a FHV challenge performed 8 weeks after vaccination. In the second study, vaccination of 8 week old cats with Purevax RC vaccine at a titre of 4.9 log 10 $CCID_{50}$ FHV provided a significant reduction of clinical signs against challenge performed 4 weeks after vaccination. Although the duration of excretion was usually reduced in vaccinates, the difference in global excretion between the vaccinates and controls was not statistically significant. Therefore, the present data do not support the claim of reduction of excretion of FHV.

The duration of protection against infectious rhinotracheitis was demonstrated for a vaccinal dose of $10^{5.3}$ $CCID_{50}$ FHV F2 that induced a significant protection against challenge carried out more than one year after second injection of primary vaccination. This protection consisted of a reduction of clinical signs and global viral excretion. Using a vaccinal dose of 5.0 log10 CCID50 FHV F2 only reduction of viral excretion was observed. However in another study, the Purevax RC vaccine at a titre of 5.0 log10 CCID50 per dose (slightly higher than the minimum recommended 4.9 log10 CCID50) for the herpesvirus component induced a significant reduction of general and local symptoms, and of global virus shedding after a herpesvirus challenge.

Considering all the data provided, the claim of reduction of clinical signs of feline rhinotracheitis is demonstrated. On the other hand the reduction of viral excretion has not been demonstrated for kittens of the minimal age recommended and administered the minimal recommended dose. This claim is, therefore, not accepted.

Protection against feline calicivirosis

The determination of the minimal protective dose for the calicivirus component was supported by two studies. A first study was performed in 10-week-old cats administered two inactivated calicivirus antigens (FCV strains G1 and 431) with an antigen content of 2.2 ELISA units and challenged by a heterologous strain 4 weeks after vaccination. The clinical score in the group vaccinated with both antigens was lower than in the control group while not statistically significant (probably due to statistical analysis including other vaccinal groups). There was no correlation between neutralising antibody titre and protection. No clear conclusion can be drawn from that study. Another study was performed in 8-9 week old cats administered the two inactivated antigens FCV strains G1 and 431 with an antigen content of 2.0 and 2.4 ELISA units and challenged by heterologous strain 4 weeks after vaccination. Both vaccines were able to significantly reduce clinical signs and viral excretion following challenge.

More than one year after vaccination, the Purevax RC vaccine with an antigen content of 2.07 ELISA units for the calicivirus component induced a significant reduction of clinical signs and of viral excretion after a heterologous FCV challenge. However, vaccination with Purevax RC vaccine with an antigen content of 2.37 ELISA units FCV induced only a significant reduction of viral excretion after challenge. Reduction of clinical signs was not statistically significant in the group receiving the highest vaccinal dose. The difference between the two vaccinated groups was, however, not significant and may be explained by the intrinsic variability of the challenge model.

Considering all the data provided, the claim of reduction of clinical signs and of viral excretion of feline calicivirosis is demonstrated.

Onset of protection

Based on the challenge studies the onset of protection is of 4 weeks for feline infectious rhinotracheitis and calicivirus infection.

Interference with maternally derived antibodies

No interference with maternally derived antibodies is expected if vaccination is performed at 8 weeks of age against FCV, FHV-1.

Field trials

Two multicentre field trials were conducted with batches of intermediate potency. In the first one, the basic vaccination schedule was applied and the second consisted of the booster vaccination being given. In both studies efficacy was based on serology.No animals of the minimum recommended age were included in the study.

The first study (basic vaccination) showed a serological response against FHV and FCV. In the second study (booster vaccination) the high antibody titres against FHV and FCV on D0 made it difficult to demonstrate the booster effect of vaccination. However, average antibody titres remained stable at a high level or increased moderately.

A major deficiency identified in the field studies was the absence of young kittens. Given the fact that the main difference between SPF and conventional kittens is the presence of MDA and considering the difficulties to recruit young kittens in field trials, a laboratory experiment was designed to induce maternally derived antibodies in SPF kittens. This laboratory trial confirmed that anti-FHV and anti-FCV MDA are not a major concern in kittens.

5. BENFIT-RISK ASSESSMENT

Purevax RC is an associated vaccine containing live and inactivated components: a modified live feline herpesvirus (F2 strain) and a combination of two inactivated purified caliciviruses (FCV431 and FCVG1 strains). . The vaccine consists of a freeze-dried pellet containing the active ingredients of feline viral rhinotracheitis and calicivirosis to be reconstituted with a solvent containing water for injection. The active ingredients of feline herpesvirus and caliciviruses are new strains in Europe.

The analytical part is well documented. The production and control of starting materials follows the recommendations of the EU note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01-Rev.1).

The results of the overdose study in cats showed transient hyperthermia occurring 4 hours after the injection and lasting certainly 24 to 48 hours, exceptionally 5 days. Hyperthermia was still observed after 72 hours in 50% of the animals. No other systemic reactions were observed. Local reactions at injection site were transient pain and swelling. A significant decrease in the number of circulating leukocytes was frequently observed. Following the repeated administration of one dose, transient hyperthermia was rarely observed. Local reactions were transient pain and swelling. Repeated injections do not amplify the adverse effects already observed following the administration of an overdose. A significant decrease in the number of circulating leukocytes was frequently observed after the second injection.

A study was carried out in cats to evaluate local safety of the Purevax RC vaccine by histology. In all injection samples, only minimal to moderate reactions could be observed. On two occasions, no reaction could be detected at histological examination. In conclusion, the local safety of the non-adjuvanted combined Purevax vaccine, administered by subcutaneous route was good and the reactions at injection site were mild to moderate. No specific study has been carried out to evaluate the impact on reproductive performance. The SPC accordingly recommends not to vaccinate pregnant animals.

Two field trials were conducted including 115 cats of different age and breed. The general reactions observed were apathy and/or anorexia, rarely hyperthermia. In most cases they were transient (less than two days). It should be noted that lethargy and apathy observed in the field were not recorded in laboratory trials. These reactions are, however, not unexpected and are appropriately mentioned in the SPC. The local reactions were pain at injection site and swelling, as already observed in laboratory trials.

No potential risk for the environment is expected.

All the efficacy trials were carried out in the feline species, in young and adult animals. The dose used in the efficacy trials had a volume of 1 ml (claimed quantity for a dose of this product). Vaccines were administered via the recommended subcutaneous route of administration, according to the schedule of vaccination. The influence of maternally derived antibodies was satisfactorily discussed.

The efficacy of the vaccine in conventional kittens of the minimal recommended age for vaccination has not been investigated considering the difficulties to perform adequate serological and challenge studies in young conventional kittens. This was considered as justified regarding the data provided on the kinetics of maternally derived antibodies (MDAs).

Vaccination of 8 week old cats with Purevax RC vaccine at a minimal titre of FHV provided a significant reduction of clinical signs against challenge performed 4 weeks and 13 months after vaccination. The effect on global virus excretion was however insufficiently documented and therefore the proposed claim on reduction of viral excretion was not supported.

The claim of reduction of clinical signs and of viral excretion of feline calicivirosis is demonstrated.

Two multicentre field trials were conducted where efficacy was based on serology.

Serological responses against FHV and FCV have been demonstrated following basic vaccination. Following booster vaccination the high antibody titres against FHV and FCV on D0 made it difficult to demonstrate the booster effect of vaccination. However, average antibody titres remained stable at a high level or increased moderately.

A major deficiency identified in the field studies was the absence of young kittens. Given the fact that the main difference between SPF and conventional kittens is the presence of MDA and considering the difficulties to recruit young kittens in field trials, a laboratory experiment was designed to induce maternally derived antibodies in SPF kittens. This laboratory trial confirmed that anti-FHV and anti-FCV MDA are not a major concern in kittens.

Therefore, it could be concluded that the vaccine is efficacious when administered as described in the SPC.

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Council Directive 2001/82/EEC.