SCIENTIFIC DISCUSSION

Name of the veterinary medicinal product:	Suvaxyn Aujeszky 783+O/W
Marketing Authorisation holder:	Fort Dodge Animal Health Holland C.J. van Houtenlaan 36 1381 CP Weesp The Netherlands
Active substances:	Live attenuated Aujeszky's Disease Virus, strain NIA_3-783
Pharmacotherapeutic group (ATCvet code):	Immunologicals for pigs, Live viral vaccine QI09AD01
Therapeutic indication(s):	Active immunisation of pigs from the age of 10 weeks to prevent the mortality and clinical signs of Aujeszky's Disease and to reduce the excretion of Aujeszky's Disease field virus. Passive immunisation of the progeny of vaccinated gilts and sows to reduce mortality and clinical signs of Aujeszky's Disease and to reduce the excretion of Aujeszky's Disease field virus.
Target species	Pigs
Withdrawal period:	Zero days

1. INTRODUCTION

Suvaxyn Aujeszky 783+O/W is a live vaccine containing the attenuated virus strain NIA_3-783. The indications for the product include the active immunization of pigs to prevent mortality and clinical signs of Aujeszky's Disease and to reduce the excretion of Aujeszky's Disease field virus. Further indications include the passive immunization of the progeny of vaccinated gilts and sows to reduce mortality and clinical signs of Aujeszky's Disease. The product is intended for intramuscular administration.

The product is presented as freeze-dried pellets in 7 ml vials of Type I hydrolytic glass, containing 10, 50 or 100 doses of the vaccine virus, plus an oil emulsion for reconstitution of the pellets in 20 ml bottles of Type I glass for 10 doses as well as in 100 ml and 250 ml bottles of Type II glass for 50 and 100 doses respectively. The product is also presented as a multipack of 10 vials with 10, 50 or 100 doses of freeze dried vaccine and ten bottles of diluent per carton box.

The product qualifies for the centralised system under Part A of the Annex to Council Regulation (EEC) No. 2309/93 as it is a medicinal product developed by means of a biotechnological process. The product contains genetically modified organisms within the meaning of Council Directive 90/220/EEC and the relevant information on the environmental risk of the product has been submitted to the satisfaction of the competent authority in The Netherlands, The Ministry of Housing, Spatial Planning and the Environment.

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

2.1 Qualitative and Quantitative Particulars of the Constituents

Composition

The product contains per dose of 2 ml:

Active substance:

Live attenuated Aujeszky's Disease Virus strain NIA_3-783: $\geq 10^{5.2}$ $CCID_{50}$*

* $CCID_{50}$ = the quantity of virus, which infects 50% of the cell cultures inoculated.

Adjuvant:

Aluminium hydroxide, Mineral oil (Marcol 52), Mannide mono oleate (Arlacel A), Polysorbate 80 (Tween 80)

Excipients:

Thiomersal

Container:

The containers of the freeze-dried component are 7-ml vials of Type I hydrolytic glass with a butyl rubber stopper and sealed with an aluminium cap.
The containers of the liquid component are 20-ml bottles of Type I hydrolytic glass and 100 ml and 250 ml bottles of Type II hydrolytic glass with a butyl rubber stopper and sealed with an aluminium cap.
The containers meet the requirements of the relevant Ph. Eur. monographs.

Product Development Studies:

The product contains a live attenuated gene deleted Aujeszky's Disease virus strain. The strain is developed at the DLO-institute for Animal Science and Health, in the Netherlands and obtained by site directed mutagenesis of the virulent strain NIA_3 following a two-step gene deletion. The first step is to delete the thymidine kinase gene of the virus, which increases its safety, the second step is to delete the glycoprotein E gene of the virus, which gives the possibility to distinguish between Aujeszky's Disease vaccine virus infection and Aujeszky's Disease field virus infection. The glycoprotein E deletion makes the vaccine strain suitable for use in an eradication programme of Aujeszky's Disease field virus in pigs as it is possible to distinguish the immunity response to vaccine virus from field virus infection.

2.2 Method of Preparation

Adequate flow-charts for all stages of the production have been presented in the dossier.

The freeze-dried component of the product is manufactured in a manner that is common for vaccines produced on cell cultures. The working cell seed is expanded until a sufficient cell substrate is obtained. The cell substrate is inoculated with the working seed virus and incubated until virus multiplication is optimal. The incubated cultures are harvested and mixed with the stabilizing solution, which stabilizes the vaccine virus after freeze-drying. The stabilized bulk harvest is filled into 7 ml vials and freeze-dried. The selection of the stabilizer based on its stabilizing properties was justified in order to increase the long-term stability of the freeze dried component and to act as a bulking agent. Data were produced to demonstrate the stability of the virus harvest for a maximum period of 24 months.

The starting point of the preparation of the liquid component of the product is an oil preparation and a water preparation followed by inclusion of aluminium hydroxide, which results in an oil-in-water emulsion.

The compatibility of the liquid component of the product with the freeze-dried component is sufficiently supported by data of several representative batches of the product. Batch to batch consistency of production is sufficiently supported by data of more than 3 representative batches of the product.

Although the product is presented in multi-dose containers, the freeze-dried component of the product does not contain a preservative system as the liquid component contains thiomersal and the recommended shelf life of the reconstituted product is 1 hour.

2.3 Control of Starting Materials

Active substances:

The gene deleted virus mutant is plaque-purified and passaged subsequently several times in secondary porcine kidney cells. This virus material is than given one further passage in a porcine kidney cell line to obtain the master seed virus which is again passaged in a porcine kidney cell line to obtain the working seed virus.

Sterility tests are carried out on master and working seed virus to control the bacterial, fungal and mycoplasmal contamination. The viral purity, the identity and the genetic stability of the molecular alterations in the virus genome are also sufficiently controlled.

Non-active substances:

The porcine kidney cell line was tested to ensure the absence of mycoplasma species and passaged at different intervals to obtain the master cell seed. The master cell seed is given further passages to obtain the working cell seed.

This master cell seed is tested to adequately control sterility against bacterial, fungal and mycoplasmal contamination. The viral purity, the identity of the animal species of origin and the karyology are also sufficiently controlled.

The other non-active substances of biological origin used for the production are sufficiently controlled and treated for sterility to ensure absence of bacterial, fungal, mycoplasma and viral contamination, in particular blue tongue virus and agents causing spongiform encephalopathies. Measures are in force to ensure that any non active substances of biological origin are in compliance with Commission Decision 534/97/EC and the CVMP Note for Guidance regarding transmission of spongiform encephalopathies.
The product was originally prepared with the stabiliser peptone for which no such reassurance had been available. Therefore, the Committee requested the Applicant as a post-marketing commitment to provide data confirming compliance with the current TSE requirements. In April 2001, the Applicant replaced peptone in the stabilising mixture with N-Z Case Plus prepared from bovine milk from Australia, New Zealand or USA. The analytical quality of vaccine freeze-dried with the N-Z Case Plus was shown to be equivalent with the vaccine freeze-dried with original peptone. Batches of the vaccine with the N-Z Case Plus met the batch safety test requirements and there was no difference in the virus titres of batches of the vaccine with the original peptone and those with the new stabiliser, N-Z Case Plus. Since there is a link between the potency and efficacy of the vaccine, it was concluded that the vaccine with the N-Z Case Plus is equally as efficacious as the vaccine with the original peptone.

2.4 Control at Intermediate Stages of the Manufacturing Process

The types of in-process control tests and the stage of manufacture at which they are carried out are adequately stated:

Freeze-dried component:

In-process control tests on determination of the cytopathic effect, bacterial and fungal sterility and the virus titration are well described.

Liquid component:

The test on the determination of the pH value is well described.

2.5 Control of the Finished Product

Freeze-dried component:

The freeze-dried component of each batch is visually inspected and adequately controlled on the following parameters: vacuum, residual moisture, bacterial, fungal and mycoplasmal sterility, viral purity, virus identity, safety and virus titer. These tests are well described and in agreement with the requirements of the monograph on Aujeszky's Disease vaccine (live) for pigs for parenteral administration, freeze-dried, of the European Pharmacopoeia (1998:0745). The batch release virus titer is $10^{5.8}$ $CCID_{50}$ per dose.

Liquid component:

The liquid component of each batch is visually inspected and adequately controlled for pH value, compatibility with the freeze-dried component, mineral oil content, aluminum content, identity and stability of the oil-in-water emulsion, thiomersal content, bacterial and fungal sterility. These tests are well described.

2.6 Stability

Freeze-dried and liquid component:

A shelf life of 12 months for the freeze dried component and 12 months for the liquid component at 2 - 8°C are sufficiently supported by data of more than 3 representative batches of the product. In April 2002, the Marketing Authorisation Holder replaced peptone in the stabilising mixture with N-Z Case Plus and provided further stability data up to 27 months for three batches of the vaccine. The results showed that a loss of virus titre mainly occurs in the first 15 months of storage and that the mean virus titre after storage for 27 months is still above the required minimum titre of $10^{5.2}$ $CCID_{50}$ per dose of the vaccine. Consequently, the MAH applied for an increase of the shelf life and the CVMP agreed to extend the current shelf life of 12 months to 2 years.

Reconstituted product:

A shelf life of 1 hour for the reconstituted product at room temperature is adequately supported by data in the dossier.

3. OVERVIEW OF PART III OF THE DOSSIER: TOXICOLOGICAL AND PHARMACOLOGICAL ASPECTS

3.1 Safety

The product is intended for intramuscular administration in the neck, in the area behind the ear to fattening pigs, gilts and sows and boars.

The vaccination schedule comprises a basic vaccination of fattening pigs and breeding pigs (gilts, sows and boars) from the age of 10 weeks followed by a second injection 3 – 4 weeks after the first injection only, in breeding pigs (gilts, sows or boars). In fattening pigs a second dose may optionally be injected 3 – 4 weeks after the first injection. For breeding pigs (gilts, sows and boars) a re-vaccination is foreseen before the first mating in gilts and during each gestation at 3 - 6 weeks before the expected date of farrowing in gilts or sows. Boars should be re-vaccinated at least every 6 months.In a whole herd system gilts, sows and boars may be re-vaccinated every 4 months.

Sufficient data from laboratory studies of the product to demonstrate the safety of a single-dose administration, an overdose administration and a repeated administration of one dose as well as the safety of reproductive performance of gilts and sows are presented. Additional data regarding the safety of the product with regard to the fertility of boars are considered to be satisfactory. Also data from laboratory studies on safety of the vaccine strain following an intranasal overdose administration and an intracerebral single-dose administration are presented. In addition data are presented on the effects of the vaccine in immunologically depressed pigs, and from studies to investigate virus spread and dissemination and the potential increase in virulence of the vaccine virus in field use.

3.2 Laboratory Tests:

3.2.1 Safety of a Single Dose

The results demonstrated a slight and transient increase in body temperature as well as a tissue reaction at the site of the injection in less than one third of pigs from the age of 10 weeks. These tissue reactions disappeared within 6 weeks. An appropriate warning has been included in the SPC and product information under “Undesirable effects”. No other clinical signs of disease or mortality occurred.

3.2.2 Safety of Repeated Administration of One Dose

The results presented show that the product is safe when given at maximum virus release titre to pigs from the recommended age of 10 weeks at repeated doses 4 weeks apart. Clinically the response was comparable to that seen when one dose was administered. The tissue reactions at the injection site disappeared after 4 weeks.

3.2.3 Safety of One Administration of an Overdose

The results presented show that the product is safe (i.e. no clinical signs of the disease were seen other than a slight and transient increase in body temperature and an icrease in the extent of tissue reactions at the site of injection) when given at maximum virus release titre to pigs from the recommended age of 10 weeks.

3.2.4 Examination of Reproductive Performance

The safety of the product was tested in breeding gilts/sows by injecting the vaccine at various stages in the pregnancy. Results demonstrated the safety of the vaccine when administered during each stage of pregnancy. There were no adverse effects seen on litter size and weight of piglets and in vaccinated pigs no increases were recorded in the number of still births, mummified foetuses or abortions.

The applicant completed an additional study, the results of which demonstrates that repeated vaccination with the product does not adversely affect the fertility of boars.

3.2.5 Safety of Immunological Functions

The applicant justifies that the product is safe regarding immunological functions in pigs.

3.3 Field Studies

Field safety studies have been carried out at several farms in the Netherlands using pigs of each recommended category and following the recommendations for use of the product. The results presented show that the product when used under field conditions is safe for each recommended category of pigs.

3.4 Special Requirements for Viruses of Live Vaccines

3.4.1 Spread of the Vaccine Strain

The results presented do not indicate that the vaccine virus spreads from vaccinated pigs to other susceptible pigs having contact with the vaccinated pigs. No evidence has been presented which suggests that the vaccine virus passes the placenta of vaccinated gilts and sows or that the vaccine virus is found in the semen of vaccinated boars.

3.4.2 Dissemination in the Vaccinated Animal

120 hours after administration of the product the vaccine virus was isolated at the injection sites. The vaccine virus was also incidentally isolated in internal organs or lymph nodes of the vaccinated pigs.

3.4.3 Increase of Virulence

The results presented do not indicate that the vaccine virus increases its virulence in any of the passages. The vaccine virus was not re-isolated after the 3rd - 4th passage.

3.4.4 Intranasal Safety

The results presented from these studies demonstrate that intranasal administration of the vaccine virus does not result in a rise in body temperature, clinical signs of disease or mortality.

3.4.5 Intracerebral Safety

Results of studies on the intracerebral safety of the vaccine virus compared with 2 other virus strains of the most common Western European Aujeszky's Disease contained in live vaccines are presented. At the dose of $10^{5.5}$ $CCID_{50}$ the neurovirulence of the 3 Aujeszky's Disease strains appear to be equal. At the dose of $10^{4.5}$ $CCID_{50}$ the mortality and/or neurological disorders are induced in 40 to 60% of the piglets. The overall results confirm no significant differences in neurovirulence between the 3 strains compared.

The data provided for the vaccine virus of the product are not however in agreement with the

requirements of the European Pharmacopoeia monograph on neurovirulence of the virus strains of live Aujeszky's Disease vaccines for pigs. However, the product is used intramuscularly and following this route of administration no vaccine virus was isolated from the brains of vaccinated pigs. Data in the published literature support the fact that the absence of the thymidine kinase gene in the Aujeszky's Disease virus increases its safety and the absence of the E-glycoprote gene in in Aujeszky's Disease virus reduces significantly the multiplication of the vaccine virus in the central nervous system of pigs.

In reaching its opinion for the product the Committee notes that after modification of the requirements of European Pharmacopoeia monograph on neurovirulence of virus strains of live Aujeszky's Disease vaccines for pigs, this monograph is still under discussion. In particular repeatability and reproducibility of the test in the monograph are being investigated. These modifications to the requirements were made on the basis of existing data generated in studies with currently authorised vaccines against Aujeszky's Disease.

The Committee concluded that the objective of the requirements in the Ph. Eur. monograph is to protect pigs from neurotropic strains of live vaccines against Aujeszky's Disease. If a vaccine strain is proven to have a sufficient safety margin in pigs, and does not multiply in the central nervous system, when used by the recommended route of administration, the objective of that monograph is considered to be attained. The Committee considered that the combination of gene deletion in the vaccine virus would adequately address the safety in the target animal. Therefore, the Committee concluded that the overall safety of the product and the route of administration of the product satisfy the objectives of the European Pharmacopoeia requirements on neurovirulence of the Aujeszky's Disease vaccine virus strains for pigs.

3.4.6 Safety in Immuno-Depressed Animals

The results presented show that the vaccine virus is safe for immuno-depressed pigs.

3.4.7 Recombination or Genomic Re-assortment of Strains

The applicant justifies that the risk of genetic re-combination of the vaccine virus with other Auieszky's Disease virus is rare and is considered to be acceptable.

3.4.8 Study of Residues

The applicant justifies that for all pharmacologically active substances Annex II entries of the Council Regulation (EEC) No 2377/90 are in existence. Therefore, the product is considered to present no risk to consumer safety. A withdrawal period of zero days is appropriate.

3.4.9 Compatibility and Interactions

No data are supplied regarding compatibility and interactions. Therefore, mixing the product with other products or administration of the product in conjunction with other medicinal products is not recommended. Appropriate warnings haven been placed in the Summary of Product Characteristics and in the product literature.

3.5 Ecotoxicity

The applicant demonstrates that the risk of exposure of the product to the environment is acceptable. A copy of the written consent of the Dutch competent authority (The Ministry of Housing, Spatial Planning and the Environment) to the deliberate release into the environment of the product containing genetically modified organisms was provided by the applicant.

3.6 User safety

The finished product contains mineral oil as adjuvant. Inadvertent injection or self-injection with mineral oil (a mixture of refined saturated liquids obtained from petroleum) has repeatedly been reported to cause necrosis, leading on some occasions to the loss of an affected digit. Inadvertent injection or self-injection may not be frequently encountered; therefore, it cannot be expected for a doctor to be immediately aware of the potential consequences of such an event. The CVMP, therefore, considered in May 2002 the need for a clear warning statement on the product literature of veterinary medicines containing mineral oil. In October 2002, the Marketing Authorisation Holder included in the SPC and the package insert a detailed warning for the user and the physian as stated in the SPC guideline for immunologicals:

"To the user:

This product contains mineral oil. Accidental injection/self injection may result in severe pain and swelling, particularly if injected into a joint or finger, and in rare cases could result in the loss of the affected finger if prompt medical attention is not given.

If you are accidentally injected with this product, seek prompt medical advice even if only a very small amount is injected and take the package insert with you.

If pain persists for more than 12 hours after medical examination, seek medical advice again.

To the physician:

This product contains mineral oil. Even if small amounts have been injected, accidental injection with this product can cause intense swelling, which may, for example, result in ischaemic necrosis and even the loss of a digit. Expert, PROMPT, surgical attention is required and may necessitate early incision and irrigation of the injected area, especially where there is involvement of finger pulp or tendon."

*For the **immediate packaging** and for the **outer carton** the following wording was added:*

"Accidental injection is dangerous – see package insert before use"

4. OVERVIEW OF PART IV OF THE DOSSIER: CLINICAL ASPECTS

The product is recommended for the active immunisation of pigs and for the active immunisation of gilts or sows to passively immunise their progeny. The adjuvant of the product contained in an oil-in-water emulsion, increases the immunizing capacity of the product through prolonging stimulation of the immunity. Data from laboratory tests regarding the onset, the level and the duration of the immunity after vaccination of pigs with and without maternal antibodies against Aujeszky's Disease are presented and address both the active immunisation of pigs and the passive immunisation of their progeny. Sufficient data from field trials are also presented.

4.1 Laboratory Studies

4.1.1 Potency and Immunogenicity of the Product

The presented results of the vaccination challenge study at the recommended dose in pigs show that the product induces sufficient clinical protection. A significant reduction in duration of excretion of a challenge virus in vaccinated pigs was seen in comparison to controls.

4.1.2 Onset of Active Immunity

The presented results of the vaccination challenge study at recommended dose in pigs without maternal antibodies against Aujeszky's Disease virus show that the product induces a sufficient active immunity within 1 week after basic vaccination.

No data regarding the onset of active immunity in pigs with maternal antibodies against Aujeszky's Disease virus are presented. This issue has been resolved in the Summary of Product Characteristics and in the product literature.

4.1.3 Degree of Active Immunity

The presented results of the vaccination challenge study at the recommended dose in pigs without maternal antibodies against Aujeszky's Disease virus show that the degree of active immunity of the product supports the claims put forward by the applicant.

4.1.4 Duration of Active Immunity

The presented results of the vaccination challenge study at the recommended dose in pigs show a duration of active immunity of 3 months after basic vaccination. Based on the level and nature of antibodies against Aujeszky's Disease, 4 and 6 months after the basic vaccination or revaccination sufficient protection can still be expected. A duration of active immunity of 6 months may be extrapolated from these data. .

4.1.5 Degree of Passive Immunity

The presented results of the challenge study with piglets from vaccinated gilts or sows show that the degree of passive immunity of the product supports the claims proposed by the applicant.

4.1.6 Duration of Passive Immunity

The presented results of the challenge study with piglets from vaccinated gilts or sows show show a duration of passive immunity of 1 week. At the age of 5 and 6 weeks the level of antibodies against Aujeszky's Disease virus is still high to expect sufficient protection. The duration of passive immunity of at least 2 months may be extrapolated from these data.

4.1.7 Influence of Maternal Antibodies

The maximal level of maternal antibodies against Aujeszky's Disease occurring in pigs at the youngest

recommended age of vaccination is not sufficiently documented. However, a negative influence of maternal antibodies against Aujeszky's Disease virus on the results of primary vaccination has been demonstrated, nevertheless immunogenicity of the product in the presence of such antibodies is still demonstrated. Therefore, this issue is resolved in the Summary of Product Characteristics and product literature.

4.2 Field Studies

Field studies have been carried out in several farms in the Netherlands using large numbers of pigs of the recommended class and age. The product was administered as recommended for use.

The duration of the trials was about 2 years and comprised approximately 320 pig herds, consisting of approximately 18 000 sows, 350 boars and 1 250 000 fattening pigs. The herds of fattening pigs were monitored for antibodies against the glycoprotein E antigen of Aujeszky's Disease virus. The sero-prevalence of field virus infected herds decreased from 81% to 19%. The sero-prevalence of field virus infected pigs in the infected herds diminished from 49% to 5%. In the controls no significant change in sero-prevalence of field virus of Aujeszky's Disease was noticed.

The results of the presented field studies show that the product is efficacious and supports the claims put forward by the applicant for each recommended category of pigs, when administered as recommended for use.

5. RISK-BENEFIT ASSESSMENT AND CONCLUSION

Overall the quality of the product has been demonstrated. The Committee noted that although the product is presented in multi-dose containers, the freeze-dried component of the product does not contain a preservative system and the recommended shelf life of the reconstituted product is therefore limited to 1 hour.

The product contains an organism within the meaning of Council Directive 2001/18/EC. The relevant information on the environmental risk of the product has been submitted to the satisfaction of the competent authority in The Netherlands, The Ministry of Housing, Spatial Planning and the Environment. Furthermore, the Applicant justified the risk of genetic re-combination of the vaccine virus with another Aujeszky's disease virus being rare. The CVMP accepted this.

The Committee discussed the objective of the requirements in the Ph. Eur. monograph regaring the protection of pigs from neurotropic strains of live vaccines. The Committee considered that the combination of gene deletion in the vaccine virus would adequately address the safety in the target animal. Therefore, the Committee concluded that the overall safety of the product and the route of administration of the product satisfy the objectives of the European Pharmacopoeia requirements on neurovirulence of the Aujeszky's Disease vaccine virus strains for pigs.

Undesirable effects observed in pigs during the safety studies included tissue reactions at the side of the injection. In the majority of cases, these tissue reactions disappear within 6 weeks after the first vaccination or within 4 weeks after the second injection or re-vaccination. An appropriate warning has been included in the SPC and product literature.

The finished product contains mineral oil as adjuvant. Since self/injection with mineral oil has repeatedly been reported to cause necrosis, leading on some occasions to the loss of an affected digit, the Marketing Authorisation Holder included in the SPC and the product literature a detailed warning for the user and the physician as stated in the SPC guideline for immunologicals.

In order to comply with the TSE requirements, the Applicant provided in April 2001 certificates of confirmity and a risk assessment. Furthermore, peptone, a substance for which such data could not be provided, was preplaced by another stabiliser.

Based on the original and complementary data presented, the Committee for Veterinary Medicinal Products concluded that the quality, the safety and the efficacy of the product are considered to be in accordance with the requirements of Council Directive 81/852/EEC and supports the claims of the applicant.

Consequently, the Committee agreed on 8 April 1998 that the product could be recommended for the granting of a Community marketing authorisation.