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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for RESPIPORC FLUpan H1N1 (EMEA/V/C/003993/0000)

Common name: porcine influenza vaccine (inactivated)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

On 29 September 2015, the applicant IDT Biologika GmbH submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for RESPIPORC FLUpan H1N1, through the centralised procedure on the basis of Article 3(2)(a) of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 8 May 2014 as RESPIPORC FLUpan H1N1 contains a new active substance (Influenza A virus/Jena/VI5258/2009 (H1N1)pdm09, inactivated) which is not yet authorised as a veterinary medicinal product in the European Union.

The rapporteur appointed is Merete Blixenkrone-Møller and the co-rapporteur is Ewa Augustynowicz.

The application for marketing authorisation has been submitted in accordance with Article 12(3) of Directive 2001/82/EC.

RESPIPORC FLUpan H1N1 was proposed for use for active immunisation of pigs against swine influenza caused by pandemic subtype H1N1 to reduce clinical signs, viral lung load and viral excretion after infection.

RESPIPORC FLUpan H1N1 was proposed in presentations as a suspension for intramuscular injection, filled in bottles of 25 ml or 50 ml. 1 ml corresponds to 1 vaccine dose.

In the light of the overall data submitted and the scientific discussion within the CVMP, a negative opinion for RESPIPORC FLUpan H1N1 inactivated vaccine for pigs was adopted, by consensus, by the CVMP on 8 December 2016.

Re-examination

On 24 January 2017, the applicant submitted written notice to the Agency to request a re-examination of the CVMP opinion of 8 December 2016. The applicant requested the involvement of a specific expert group in the re-examination.

The rapporteur appointed is N. Garcia del Blanco and the co-rapporteur is J.G. Beechinor.

The CVMP agreed to the establishment of a specific Ad Hoc Expert Group (AHEG). The AHEG consisted of experts in auditing of clinical studies/study design, quality of vaccines, and in swine influenza.

In the light of the scientific data available and the scientific discussion within the Committee, the CVMP re-examined its initial assessment concerning the points raised in the grounds for re-examination.

On 16 March 2017, the CVMP adopted a positive opinion, by majority, and CVMP assessment report.

On 17 May 2017, the European Commission adopted a Commission Decision granting the marketing authorisation for RESPIPORC FLUpan H1N1.

Scientific advice

The applicant did not seek scientific advice at the CVMP.

MUMS/Limited market status

Not applicable.

Initial assessment

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (version 008, dated 23 July 2014) which fulfils the requirements of Directive 2001/82/EC.

Based on the information provided, the applicant has the services of a qualified person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the European Union or in a third country.

Manufacturing authorisations and inspection status

RESPIPORC FLUpan H1N1 is manufactured by IDT Biologika GmbH, Dessau-Rosslau, Germany.

Secondary packaging and batch release for the EU will be carried out by IDT Biologika GmbH as well.

The site has a manufacturing authorisation issued on 4 February 2014 by the Land Administration Office of Saxony-Anhalt (Germany). GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided.

A GMP declaration for the active substance manufacturing site was provided from the QP at the EU batch release site. The declaration was based on an on-site audit of the manufacturing site responsible for batch release.

Overall conclusions on administrative particulars

A detailed description of the pharmacovigilance system and the GMP certification of both the active substance and finished product manufacturing sites were considered in line with legal requirements.

Part 2 – Quality

Composition

RESPIPORC FLUpan H1N1 is an inactivated monovalent viral vaccine for active immunisation of pigs against swine influenza caused by influenza A virus (FLUAV) subtype (H1N1)pdm09, where pdm 09 refers to the pandemic spread detected in 2009. The vaccine virus, FLUAV/Jena/MSV-VI5258/2009 (H1N1)pdm09 originates from a human isolate of July 2009.

RESPIPORC FLUpan H1N1 is presented as a suspension for intramuscular injection, filled in bottles of 25 ml or 50 ml. 1 ml corresponds to 1 vaccine dose. The active substance of this product is a pandemic influenza A virus FLUAV/Jena/MSV-VI5258/2009 (H1N1)pdm09. The quantity of the active substance was originally proposed to be a minimum of 8 haemagglutination units (HU) and a maximum of 64 HU but later the minimum potency was proposed to be changed to 16 HU. Thiomersal is added as preservative, carbomer 971 P NF is added as adjuvant and the diluent is sodium chloride solution (0.9%).

Container and closure

The vaccine is filled into 25 ml or 50 ml polyethylene terephthalate (PET) bottles (in accordance with European Pharmacopoeia (Ph. Eur.) chapter 3.2.2.1.). These are closed with siliconised bromobutyl rubber stoppers (in accordance with Ph. Eur. Chapter 3.2.9.) and aluminum flanged caps. Specifications and certificates demonstrating Ph. Eur. compliance were provided for the bottles and stoppers.

Development pharmaceutics

A detailed report on the development of the vaccine RESPIPORC FLUpan H1N1 with regard to composition, components and containers supported by scientific data has been presented.

Information has been provided on the choice of vaccine strain, adjuvant carbomer and the preservative thiomersal. The information is satisfactory.

Either binary ethyleneimine (BEI) or KOH stabilised ethyleneimine (EI) is used for the inactivation. A validation report for the inactivation kinetics was shown for both BEI and EI.

A haemagglutination assay (HA) was chosen for measuring the potency. The test works by measuring the haemagglutinating activity in the vaccine. A value of 16 HU was chosen as minimum potency.

The choice of a HA for determination of potency might be acceptable, however, the accuracy of the method as it has been described in the section ‘Control Tests on the finished product’ is not considered acceptable. The accuracy of the potency test is not considered acceptable due to the limited information provided in the validation report. The capacity of the test to distinguish between potent and sub-potent vaccine batches is not clearly established.

Method of manufacture

The manufacturing process is based on the seed lot system and a detailed description of the manufacturing process is presented. In summary, the manufacturing process consists of the following steps: cell cultivation, virus production, virus harvest, clarification filtration of the virus harvest, virus inactivation, batch formulation, filling and packaging.

The manufacturing process has been validated. A validation report for the inactivation kinetics shows that the virus strain is inactivated in accordance with Ph. Eur. monograph 0062. The validation of the inactivation kinetics is therefore considered acceptable.

Control of starting materials

Active substance

The active substance has been controlled for sterility and absence of mycoplasma, pH, antigen

content, content of adjuvant and preservative, virus inactivation, free sodium thiosulphate and filling volume. The following methods are in accordance with Ph. Eur. Sterility (Ph. Eur. 2.6.1 – direct inoculation), pH measurement (Ph. Eur.2.2.3 – potentiometric determination) and test for presence of mycoplasma (Ph. Eur. 2.6.7). The results show that the control of the active substance is satisfactory.

Stability of the active substance

Stability data for three batches of the live virus, stored for 5-6 months, has been provided. The data demonstrate that the live virus can be stored for 6 months at 2–8 °C prior to inactivation.

Stability data has been presented for storage of three batches of the clarified filtrate. The data supports a storage time of 7 days at 2–8 °C for the clarified filtrate.

Stability data has been presented for four batches of the bulk blend. The data confirms a storage time of 14 days at 2–16 °C.

Additionally, a storage time of 5 months for the inactivated/neutralised bulk has been demonstrated for three batches.

It is observed for some of the batches of inactivated/neutralised bulk that there is a significant titre decrease during storage. The reasons for this loss in HU content have been investigated and it was found that the decrease in HU content correlates with an increase in pH. The apparent instability of the bulk antigen is of a major concern and cannot guarantee a consistently manufactured active ingredient.

Excipients

Starting materials listed in the European Pharmacopoeia

A list of starting materials of non-biological origin, listed in the Ph. Eur., is presented. All these starting materials are stated to comply with the current edition of the Ph. Eur.

Starting materials not listed in the European Pharmacopoeia

A list of starting materials not listed in the Ph. Eur is presented.

The master seed virus (MSV) and working seed virus (WSV) are tested according to the requirements of Ph. Eur. 0062 “Vaccines for veterinary use”, and also the CVMP Guideline on requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010) for sterility, absence of mycoplasma, absence of mycoplasma DNA, contamination with viruses, identity and virus titre. Certificates of analysis for the MSV and WSV and standard operating procedures (SOP’s) for the test methods are presented.

A risk analysis is presented to justify the extent of tests that should be performed to ensure the absence of extraneous agents. Based on this risk analysis absence of relevant extraneous viruses was determined using the general and specific tests as described in the Ph. Eur. The following tests have been performed on the master cell seed (MCS): microscopy (growth characteristics, morphology), sterility, absence of mycoplasma, contamination by extraneous viruses, absence of mycoplasma DNA in the cell culture, identity and karyotype.

The following tests are performed on the working cell seed (WCS): microscopy (growth characteristics, morphology), sterility, absence of mycoplasma, contamination by extraneous viruses, and absence of mycoplasma DNA in the cell culture.

To justify which extraneous agents needed to be tested in the cell line, a risk analysis was compiled and was considered acceptable.

The quality of the foetal calf serum is tested by the suppliers in accordance with Ph. Eur. requirements and in-house for identity within the scope of incoming goods. The serum is gamma-irradiated. Certificates of analysis and validation studies of serum inactivation by gamma-irradiation are provided.

Certificates of analysis are presented for other starting materials of biological origin. The in-house prepared solutions are either steam sterilised or sterilised by membrane filtration when they cannot be autoclaved because they are heat sensitive. The solutions sterilised by membrane filtration are tested for sterility.

The list of excipients is proposed for inclusion in section 6.1 of the proposed SPC.

In conclusion, starting materials used in the production of the vaccine are satisfactorily described and in compliance with the requirements of Ph. Eur. Starting materials not listed in a pharmacopoeia and in-house media are also described including relevant and acceptable control tests.

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

A risk assessment is presented for the virus seed materials and the cell line.

The starting materials of biological origin comply with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01-Rev.3). Valid TSE certificates of suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) have been presented for all the suppliers of the starting material foetal calf serum. No TSE certificates are available for the foetal bovine serum or the bovine serum used for the first passages of the cell line. This is however acceptable as the cell line was established in the 1950's.

The TSE risk is considered negligible.

Control tests during production

The in-process controls established during the individual production steps in the production process of RESPIPORC FLUpan H1N1 are all described in detail in the dossier. The in-process controls are considered appropriate, and in line with the expectation for a veterinary vaccine, to assure a well-controlled and consistent production process. The following in-process controls are performed: antigen content, sterility and absence of mycoplasma, control of pH, control of virus inactivation, control of fill weight and content of carbomer and thiomersal.

BEI or KOH stabilised EI is used for virus inactivation. The inactivation is performed in accordance with Ph. Eur. 0062 and 0963. After inactivation, sodium thiosulphate solution is added to the virus suspension for neutralisation of the ethyleneimine. The detection of free sodium thiosulphate proves the complete neutralisation of the inactivating agent ethylenimine. A test for free thiosulphate is included as in-process control. The test for in-process proof of inactivation is highly sensitive. It is suited for usage as in-process control and ensures proof of inactivation.

Batch-to-batch consistency show that the in-process controls are well within the acceptance criteria, and they support that the manufacturing process is able to produce batches of consistent quality.

Control tests on the finished product

The description of the methods used for the control of the finished product (appearance, pH value, content of adjuvant and preservative, sterility, inactivation, safety, absence of extraneous viruses and potency) and the specifications were provided.

The potency test works by measuring the specific haemagglutinating activity in the vaccine. The haemagglutinin represents one of the main antigens of the influenza virus.

Positive and negative controls are included in each test to confirm the validity of the test. The capacity of the test to distinguish between potent and sub-potent vaccine batches is however not clearly established. Further information on the potency specifications should be presented taking into account the variability on the level of antigen recorded during the real time stability studies. Statistical analysis should be revaluated to decrease the level of variability of the calculations with the appropriate statistical tools.

A release potency of at least 32 HU has been proposed, to compensate for potential inaccuracy and the minimum potency at the end of shelf–life has been increased from 8 HU to 16 HU. At least two out of three batches have to have a potency of at least 32 HU, at the time of release. The accuracy of the potency method remains insufficiently demonstrated by the data included in the dossier. Further raw data on the validation of the potency test method are missing.

The results of the analysis of three consecutive production runs of the vaccine were presented which comply with the required specification, and support that the quality of the vaccine is consistent from batch to batch.

Stability of the finished product

A shelf-life of 24 months based on 27 months long-term stability on three batches with a minimum potency of 8 HU was initially considered acceptable. However, the minimum potency was revised and set at 16 HU and the minimum release titre set at 32 HU.

The data of the three batches can no longer be used to set the shelf-life. This is based on the fact that the new minimum release titer is now set at 32 HU, and the aforementioned batches were released with a potency of 16 HU. Two other batches were also released at 16 HU and 3 months stability data was presented for these two batches.

Stability data for two additional batches at 32 HU (the new minimum release specification) have been presented. For one batch only potency data are shown. No other stability data have been presented for this batch, therefore it cannot be confirmed if the other parameters tested during stability are within the specification limits. The other batch was shown to be just supportive data, as potency only has been measured at release and after 36 months. Additionally, it has not been stated anywhere how these two batches are stored.

Taking all these issues into account as well as the proposed minimum potency of 16 HU, a 3 months shelf-life is acceptable on the basis of data provided.

The proposed restriction in storage conditions, concerning protection from light can be accepted.

The efficacy of the thiomersal preservative has been tested on two batches of vaccine and it met the requirements of Ph. Eur. 0062.

Environmental risk assessment for products containing or consisting of genetically modified organisms is not applicable.

The efficacy of the thiomersal preservative has been tested on two batches of vaccine and meets the requirements of Ph. Eur. 0062. On the basis of data provided the in-use shelf-life should be limited to 10 hours.

Overall conclusions on quality

The development, manufacture and control of the active substance and finished product of RESPIPORC FLUpan H1N1 is partly presented in a satisfactory manner. A validation study was provided for inactivation kinetics which can be considered as appropriately validated.

Starting materials used in the production of the vaccine are satisfactorily described and in compliance with the requirements of Ph. Eur. Starting materials not listed in a pharmacopoeia and in-house media are also described including relevant and acceptable control tests.

Production and testing of the MSV and WSV are clearly described. SOPs have been provided describing all testing.

The risk of transmitting transmissible spongiform encephalopathy (TSE) infectivity through the use of this vaccine is negligible.

The in-process tests for the vaccine are described satisfactorily.

A 3 months shelf-life is acceptable on the basis of data provided.

Generally, the quality part of the dossier is detailed and complies with relevant monographs and guidelines.

However, there are areas of quality where data provided are incomplete:

- The validation of the potency test method remains insufficiently demonstrated by the data included in the dossier.

  Further information on the potency specifications should be presented taking into account the variability on the level of antigen recorded during the real time stability studies. A statistical analysis should be performed on the existing data with the aim to decrease the level of variability of the calculations with the appropriate statistical tools.

- On the basis of data provided for some of the batches of inactivated/neutralised bulk there is a significant titre decrease during storage. The reasons for this loss in HU content have been investigated and it was found that the decrease in HU content correlates with an increase in pH. It has not been clarified why the pH is increasing during storage for the inactivated antigen bulk, causing the HU content to decrease.

In conclusion, the data does not support the production of consistent and stable batches of active ingredient due to the variation in observed pH of the active ingredient over the period storage of the bulk antigen. In addition, the proposed potency assay is subject to much variation and therefore the antigen content in the bulk antigen cannot be determined with confidence. The validation of the method remains insufficiently demonstrated by the data included in the dossier.

Part 3 – Safety

The safety of RESPIPORC FLUpan H1N1 was evaluated according to general requirements.

Requirements for immunological veterinary medicinal products as described in Directive 2001/82/EC, Guideline on requirements for the production and control of immunological veterinary medicinal

products (EMA/CVMP/IWP/206555/2010) and the relevant monographs of the Ph. Eur. ("Porcine influenza vaccine (inactivated)" (04/2013: 0963), "Vaccines for veterinary use" (04/2013: 0062) and "5.2.6.: Evaluation of safety of veterinary vaccines and immunosera" (04/2013: 50206)).

RESPIPORC FLUpan H1N1 is proposed for use for active immunisation of pigs against swine influenza caused by Influenza A virus (FLUAV) H1N1 pandemic 2009 subtype to reduce clinical signs, viral lung load and viral excretion after infection.

The vaccine is intended for intramuscular (i.m.) injection to be applied as follows:

Primary vaccination:

1st immunisation: 1.0 ml i.m. from the age of 56 days on;

2nd immunisation: 1.0 ml i.m. 3 weeks after 1st immunisation.

Laboratory tests

The laboratory tests for safety were performed in accordance with the principles on Good Laboratory Practice (GLP). A vaccine batch containing the maximum potency (64 HU) was used.

The requirements to be considered in the laboratory studies were in accordance with the Ph. Eur. monographs “Porcine influenza vaccine (inactivated)” and “Evaluation of safety of veterinary vaccines and immunosera”.

The batches used for safety testing were produced according to the manufacturing process.

The vaccine was administered by the recommended route of administration (i.m.) to animals close to the minimum age of administration (56 days) and without maternal antibodies to swine influenza virus of the subtype included in the vaccine. Pigs of normal commercial breeds were used in the studies.

The animals were observed and examined for 14 days after each vaccination for signs of systemic and local reactions.

Safety of the administration of one dose

Safety of single and repeated administration of a single dose

The study provided on safety of single and repeated administration of a single dose involved 16 vaccinated pigs and 16 control pigs. The placebo control pigs were vaccinated with a formulation containing excipients without the active ingredient. The pigs of groups 1 and 2 were vaccinated on Day (D) 0 and D14 with vaccine of maximum potency (64 HU) and placebo-vaccine, respectively.

The follow-up after vaccination consisted of daily examinations for clinical signs and for local reactions (scoring system used). Rectal body temperatures were measured from 2 days before vaccination, on the day of vaccination and 2 hours, 4 hours, 8 hours, daily until D18 and on days 21 and 28 after vaccination. Weight was measured at days 0, 7, 14 to 18, 21 and 28. After euthanasia on D28, necropsy and histological examinations were made of tissue samples from the injection sites. Blood samples were taken on days 7, 11 and 28 for testing for antibodies against FLUAV(H1N1)pdm09 by haemagglutination inhibition test (HI).

No clinical signs with direct correlation to the administration of the vaccine were observed. Minor local reactions at the injection site in the form of swellings below 1 cm were observed (mostly after second vaccination) and a possible transient increase in temperature. Mild to moderate microscopic lesions

were noted in 8 and 5 pigs of groups 1 and 2, respectively. Mean weight gain was similar between the groups.

Warnings of minor transient local reactions and minor transient temperature increases are proposed for inclusion in section 4.6. of the SPC. A transient increase in rectal temperature, not exceeding 2 °C, is common after vaccination and this does not persist for more than one day. A transient swelling up to 2 cm^3 may occur at the site of injection; these reactions are common but resolve within 5 days.

On the basis of the above it can be concluded that a single dose and a repeated dose of the vaccine did not reveal reactions eliciting any significant safety concerns.

Safety during the onset of immunity (OOI) study after primary immunisation

A laboratory efficacy study was provided in which the safety parameters of the vaccine were also monitored. The study was not carried out to GLP and a minimum potency of 16 HU (quality issues of batch used) was stated to be used. While findings indicative of a safety concern were hot detected, the study can only be considered supportive.

Safety of one administration of an overdose

According to Directive 2001/82/EC, overdose testing is required only for live immunological veterinary medicinal products. Since the product does not qualify as a live immunological veterinary medicinal product, an overdose safety study has not been conducted.

Safety of the repeated administration of one dose

The safety of one repeated administration of a single dose of the product was investigated in one study. The study has been summarised above.

Examination of reproductive performance

No studies have been undertaken as the vaccine is intended only for use in pigs from 56 days of age.

Examination of immunological functions

No investigations were carried out on the effect of the vaccination with RESPIPORC FLUpan H1N1 on the immunological functions. However, for an inactivated whole virus, adjuvanted vaccine against influenza A, such investigations are not considered necessary.

Study of residues

The active substance of biological origin intended to produce active immunity does not fall within the scope of Regulation (EC) No 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin. Therefore, no specific study of residues has been carried out.

The excipients, including the adjuvant, are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no maximum residue limits (MRLs) are required, or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

The withdrawal period is set at zero days.

Interactions

No data were provided to investigate interactions of the vaccine with other veterinary medicinal product. Accordingly, it is proposed that the SPC include to the effect no information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal products. Appropriate warnings are proposed to be included in the proposed SPC Section 4.8.

Field studies

The results from the laboratory trials were supplemented by data from field trials. The study objective of the field trials was to demonstrate that the repeated administration of a single dose of RESPIPORC FLUpan H1N1 is safe in pigs of the youngest recommended age.

Two field studies to evaluate the safety of RESPIPORC FLUpan H1N1 under field conditions according to Ph. Eur. monograph 0963 and in accordance with Good Clinical Practice (GCP) requirements were submitted.

One study was performed to test the safety of repeated administration of a single dose of RESPIPORC FLUpan H1N1. The study was randomised, placebo-controlled and in accordance with GCP requirements. Pigs were vaccinated at the age of maximum 56 days and 21 days later. 95 pigs in group A were administered RESPIPORC FLUpan with a potency of 16 HU and other 95 pigs in group B were administered sodium chloride. The use of minimum potency batches would not be satisfactory for laboratory studies but for a field safety study it may be acceptable as representative of a typical manufactured batch.

Another study was performed to test the safety of RESPIPORC FLUpan H1N1 in pigs under field conditions. The study was randomised, placebo-controlled and in accordance with GCP. Group A (n=42 pigs) was administered RESPIPORC FLUpan H1N1 with a minimum potency of 16 HU and group B (n=42) was pigs administered sodium chloride. The pigs were treated twice at the age of 50 days and 3 weeks later.

In addition, a third field trial was performed involving 160 pigs. The vaccination schedule of the field study, with first vaccination at the average age of 45 days and a 2nd vaccination 3 weeks later, which is not in line with the minimum recommended age for vaccination (day 56). As the potency of the vaccine at the time of use was not stated in the study report, no conclusions of relevance to the RESPIPORC FLUpan H1N1 can be taken from this study.

It is concluded that the use of vaccine RESPIPORC FLUpan H1N1 in pigs of the youngest recommended age (56 days) with a repeated i.m. administration at an interval of 21 days did not reveal reactions eliciting safety concerns. No abnormal increase of rectal body temperature, no local and systemic adverse reactions occurred after vaccination. There was no statistically significant difference between groups regarding body weight over the study period from D0–D35. Field studies were documented to be carried out with batches of minimum potency (16 HU). This approach for determining field safety with a representative batch even at minimum potency is considered acceptable, considering that the laboratory safety study did not suggest safety concerns. The potency of batch when used in study has not been stated in the study report. This is not acceptable, given that the potency of the batches has been documented to change over time, potency at time of use should be documented for a sound scientific approach.

In the final report from “Field studies to test the safety and efficacy of the repeated administration of a single dose of RESPIPORC FLUpan H1N1” vaccination of sows (140,605), piglets (26,395) and fatteners/gilts (29,532) in a total of 277 farms with a mean farm size of 535 sows were carried out.

Several different batches of unstated potency were used (so-called typical commercial batches were used. The individual adverse events (AEs) from eight reports in total were fever, cough, loss of appetite, increase in abortion rates, return to oestrus, and increased level of diarrhea in sows at farrowing. The respiratory AEs were non-specific, and porcine reproductive and respiratory syndrome virus (PRRS), porcine circovirus type 2 (PCV2) and other pathogens were isolated in the herds as well. AEs such as abortion and return to oestrus are not relevant to this application at present, as the applicant did not apply for sows as target group.

As the potency of the batches used in these field investigations has not been detailed, the relevance of these data for the purposes of establishing safety of the product to be marketed is unclear.

User safety

A user safety assessment compliant with the CVMP Guideline on user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006) was provided.

There are no serious risks expected to the user from this formulation. The vaccine is inactivated and does not contain infectious microorganisms; hence although influenza caused by Influenza A virus subtype H1N1pdm09 is a zoonosis the vaccine does not present a zoonotic hazard to the user.

With appropriate use of the vaccine, direct contact with the vaccine is unlikely. As with any injectable product there is a risk of self-injection. In case of accidental self-injection only a minor injection site reaction is expected.

The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the intended recommendations.

Environmental risk assessment

A risk assessment has been provided in compliance with the CVMP Guideline on the environmental risk assessment of immunological veterinary medicinal products (EMEA/CVMP/074/95).

Hazard identification:

RESPIPORC FLUpan H1N1 is an inactivated vaccine and does not contain any live organisms.

Sterility is tested on the finished product so that problems with extraneous organisms can be excluded.

The vaccine contains carbomer as adjuvant and thiomersal as preservative. Thiomersal contains ethyl mercury and is included in Commission Regulation (EU) No 37/2010 for use only as preservatives in multidose vaccines at a concentration not exceeding 0.02%. Naturally occurring mercury compounds are known to be toxic and accumulate in the body and environment and remain for a long time. The mercury compound of thiomersal is a different form of mercury i.e. ethyl mercury, which is metabolised and removed from the body much faster than is methyl mercury and quantities present in the vaccine are very small.

Exposure to hazard:

RESPIPORC FLUpan H1N1 is administered intramuscular.

The target animals are vaccinated twice with a single dose of 1.0 ml with an interval of three weeks.

The i.m. injection of a single dose is to be given to each animal separately. Therefore, the vaccine should not contaminate the environment directly but the content of a bottle may be spilled.

Thiomersal is listed in Table 1 of Commission Regulation (EU) No 37/2010 and approved for use in food producing species only as preservative in multidose vaccines at a concentration not exceeding 0.02%. Carbomer is considered as not falling within the scope of Council Regulation (EC) 470/2009.

A single dose of the vaccine (1.0 ml) introduces only very small quantities of these substances into the animals and also the environmental risk from the use of the vaccine is assessed as negligible.

Based on the data provided, the ERA can stop at Phase I. RESPIPORC FLUpan H1N1 is expected to pose a negligible risk for the environment when used according to the intended recommendations.

Overall conclusions on the safety documentation

The safety of the vaccine has been assessed in one GLP laboratory study and in 2 GCP field studies.

The laboratory study was undertaken with the pigs of the minimum age free from maternal antibodies with a repeated i.m. administration. The maximum potency of the vaccine (64 HU) was used in the pivotal laboratory safety study.

The single and repeated administration of a single dose resulted in no significant clinical signs. Minor local reactions at the injection site were observed (mostly after second vaccination) and a possible transient increase in temperature. Mild to moderate microscopic effects at the injection site were noted. Mean weight gain was similar between the groups.

Warnings of minor transient local reactions and minor transient temperature increases are included in the proposed SPC.

No studies were performed to evaluate the safety of one administration of an overdose or the immunological functions. This is considered acceptable as there is no requirement for determining an overdose of an inactivated vaccine and it is not expected that such a product would have any adverse effects on immunological functions.

The results from the laboratory trials were supplemented by data from two field trials. A third field study was not acceptable as the potency of the relevant vaccine was not stated in the study report.

Based on the results of the field studies, it is concluded that the use of vaccine RESPIPORC FLUpan H1N1 in pigs of the youngest recommended age (56 days) with a repeated i.m. administration at an interval of 21 days is generally well tolerated.

No residues studies are required.

The withdrawal period is set at zero days.

The user safety has been adequately addressed. The user safety for this product is acceptable when used as recommended in the proposed SPC.

Based on the data provided the ERA can stop at Phase I. RESPIPORC FLUpan H1N1 is expected to pose a negligible risk for the environment when used according to the intended recommendations.

Part 4 – Efficacy

Introduction and general requirements

RESPIPORC FLUpan H1N1 is an inactivated, adjuvanted viral vaccine proposed for the active immunisation of pigs against swine influenza caused by influenza A virus (FLUAV) H1N1 pandemic 2009 subtype.

Efficacy should be demonstrated in compliance with Directive 2001/82/EC, the European Pharmacopoeia (Ph. Eur.) chapter 5.2.7, and the specific Ph. Eur. monograph (0963: Porcine Influenza Vaccine (inactivated)).

The CVMP would highlight from the outset that throughout the procedure the CVMP expressed significant reservations regarding the quality of the documentation submitted by the applicant for the efficacy studies. The applicant also acknowledged the shortcomings in the quality of the three submitted (laboratory) efficacy study reports.

Key elements of basic quality assurance (QA) have not been respected.

In the case of the RESPIPORC FLUpan H1N1 an internal investigation was undertaken by the applicant during the procedure to further investigate and reconfirm the application of appropriate quality assurance standards to the concerned studies and study reports. The investigations identified many deficiencies in the conduct and reporting to the efficacy studies concluding that that the quality of the study reports did not meet their own expectations for the level of QA. However, the applicant considered that the raw data of the studies was robust and accurate and could be trusted to provide data for evaluating the efficacy of the product.

The applicant also commissioned a separate QA audit of the data used for all efficacy study reports by a QA department of an external company. As a consequence audit study reports were amended. The amended study reports were subsequently reviewed and signed by the applicant, concluding that the corrections were considered not to have any impact on the quality of raw data and, therefore, the efficacy evaluation of the vaccine.

The CVMP noted that the applicant had submitted revised reports containing substantial additional information or changes. CVMP has serious concerns on the quality of the documented reports however, in the interests of a thorough scientific evaluation all amended reports were assessed on the basis that they were accurate and reliable. Despite the above significant reservations as identified above regarding the quality of the documentation submitted, the CVMP assessed all data available to it and observed major deficiencies which are described in the efficacy sections of this report. In conclusion, key elements of basic QA have not been respected for the submitted efficacy reports in support of the marketing authorisation application. In the absence of the full confidence of the reliability of the efficacy data, reliable conclusions cannot be drawn from those studies concerning efficacy. Considering that these studies are a fundamental requirement for the demonstration of efficacy, the deficiency is significant.

Efficacy parameters and tests

The chosen efficacy parameters of laboratory studies were viral load in the lungs, virus excretion and dyspnoea score. In addition body temperatures and body weights were provided.

An HI assay and serum neutralisation assay (VNT) were used to investigate specific serological responses.

Efficacy documentation

Studies conducted to investigate the efficacy of the product included 4 laboratory studies, two studies at OOI, one duration of immunity (DOI) study, and one study on the efficacy of vaccination in the face of maternally derived antibodies (MDA). In addition, three combined safety and efficacy field trials were performed and an amended study report regarding a combination of field study with laboratory challenge was conducted.

Key elements of QA have not been respected.

The aerosol challenges of the 4 laboratory studies were carried out in GLP certified infection units. Three of four laboratory studies were carried out in accordance with the proposed minimum age of 56 days recommended for vaccination, while for MDA study vaccination started at the age of 3 days. For the latest added study vaccination was carried out with the proposed minimum age of 56 days.

For one of the three field studies vaccination was carried out in compliance with the proposed minimum age for vaccination, while for the two other field studies, vaccination was initiated at the age of 45 days and 50 days. Serological response following vaccination was investigated in the three field studies.

Notably, field efficacy investigations after natural exposure to influenza A virus (H1N1)pdm09 have not been investigated.

In one field study it was demonstrated that at the age of 50–52 days up to 20% of pigs may still present MDA due to the vaccination of sows with RESPIPORC FLU 3 (which contains other subtypes of influenza A virus) and/or due to the previous influenza A virus (H1N1)pdm09 infections. The MDA interfered with HI antibody responses after vaccination.

The quantity of the active substance was originally proposed to be a minimum of 8 HU but later the minimum potency was proposed to be changed to 16 HU. All batches used for efficacy testing were stated to be manufactured according to GMP and according to the manufacturing process proposed for commercial batches, and signed GMP documents have been presented. The accuracy of the potency testing method has not been adequately determined which makes interpretation of potency of vaccines used in clinical studies impossible and the efficacy results cannot be correctly assessed. Information on the vaccine batch and its potency used for field study has not been provided.

Laboratory trials

The following laboratory studies were provided: dose finding of vaccine antigen and OOI at 7 days after finished primary immunisation, OOI at 7 days after finished primary immunisation, and DOI over 3 months after finished primary immunisation. In addition, one study investigating vaccination from day 3 of life in the face of MDA was provided.

Establishment of a challenge model

An aerosol challenge exposure was used and is considered suitable for the purpose of experimental challenge. However, the level of the aerosol challenge was not empirically determined but estimated by calculation.

Taken together, the technical aerosol challenge set-up would mimic natural influenza A virus exposure and is appropriate for challenge with virulent influenza A virus (H1N1)pdm09. Importantly aerosol challenge should be less stressful for the animals compared to the intratracheal exposure stipulated in the Ph. Eur. 0963.

Groups of animals of each challenge exposure were housed in the same room during aerosol challenge procedure, and were considered to receive as close as practically possible challenge under identical aerosol challenge conditions.

Vaccine and challenge strains

Information has been presented on the full sequence data of the vaccine strain (MSVVI5258) and parental strain (A/Jena/VI5258/2OO9). It has been confirmed that these strains are both influenza

A/H1N1pandemic 2009 viruses; all segments correspond to A/California/04/2009 with no data to indicate reassortments have been identified. The same conclusion was reached with the second challenge strain A/swine/Schallern/IDT19989/2014. This is also an influenza A/H1N1 pandemic 2009 virus; all segments correspond to A/California/04/2009 and data indicating reassortment have not been identified.

For the most recently presented combined field and laboratory challenge study the strain influenza A virus/sw/Teo (Spain)/AR641/16 (H1N1)pdm09 was used. Issues concerning the antigenic characteristics and virus passage history were not provided at the time of submission.

Overall, investigated influenza A virus (H1N1)pdmH1N1 isolates (vaccine and the principal challenge strains used at OOI and DOI studies) are very similar when presented in the phylogenetic analyses (Lewis et al. 2016, eLife 2016;5:e12217).

Conclusion on vaccine strain

Nucleotide sequence data support, that the FLUpan vaccine strain was considered related to the current epidemiological situation in EU at the level of phylogeny concerning the important hemagglutinin and neuraminidase genes.

Conclusion on challenge strains

The relevance of the human challenge strain used in the vaccine dose titration study was acceptable to establish the correlation between virus lung load and vaccine dose and it was important that representative porcine strains were used to establish the OOI and DOI.

In the critical challenge studies the challenge viruses were of porcine origin relevant to the current EU epidemiological situation for pandemic H1N1 circulating in pig population. However, it was noted that the challenge viruses did not routinely cause clinical signs in infected pigs.

Onset of Immunity (OOI)

Three studies were carried out in pigs age of 53–56 days to investigate the onset of protection, by the recommended administration route. The challenge was carried out on day 7 days after primary immunisation.

One study was described in the 'Additional Study' section of this report and was provided at a late stage of the application. It was a combined field and efficacy laboratory study.

Dose finding of vaccine antigen and OOI study

In this study the vaccine and placebo were administered twice with a single vaccine dose (1 ml) with variable antigen content at a three-week interval to seronegative pigs in eight groups (N=13). The number of animals in the vaccinated and placebo/control groups complies with the minimum 10 animals in each of the groups as stipulated in the specific Ph. Eur. 0963.

Groups 1 to 6 were administered the test product with the following corresponding potency (HU groups: 64 (group 1), 16 (group 2), 8 (group 3), 4 (group 4), 2 (group 5), 1 (group 6). Group 7 was a placebo-vaccinated group, and group 8 was a positive vaccine control (an older batch QC tested at 32 HU). The first dose of vaccine was administered at 54 days of age which is close to the proposed minimum age of 56 days. Concerning the minimum age and serological status (seronegative), the pigs represent the most sensitive target group. One week after completing the primary vaccination of two doses all pigs were challenged by aerosol administration of a virus strain originally isolated from a man in 2009 FLUAV/Hamburg/NY1580/2009 (H1N1)pdm09.

The aerosol challenge appeared to have been effective as infectious virus was isolated from lungs of pigs sacrificed on D1 and from some of the pigs sacrificed at D3 post challenge.

The efficacy parameters chosen were virus load in lungs, and dyspnoea scores. In addition data on body temperature, body weights, and induction of virus specific antibodies were provided. Data on viral load in nasal swaps was presented in a later version of the study report, while the study plan did not include the collection of the nasal swabs until a revised version was submitted following an internal investigation included this data.

Results

The serological response measured in the VNT showed an overall dose-dependent correlation with the determined HU content of the vaccine in this titration study. Vaccines containing ≥8 HU of antigen induced baseline detectable levels of neutralising antibodies in 77–100% of the immunised pigs.

Viral load in lungs of the pigs were investigated on D1 and D3 after infection which appear to be close to the 24 and 72 hours stipulated in Ph. Eur. 0963. Groups vaccinated with vaccine batches of 8 HU and below exhibited viral lung loads of around 7.6–8.5 log $TCID_{50}$/10g on D1 after challenge. These virus loads were in the high end of the range when compared to the viral lung load of the controls (mean titers of 9.7 log $TCID_{50}$/10g).

For D3 after infection vaccination with 8 HU (group 3) resulted in an average viral lung load of circa 5.2 log $TCID_{50}$/10g lung tissue. No significant reduction in viral lung loads was observed for 4 HU (group 4) when compared to the controls which means that compliance with the Ph. Eur was not met for the vaccine with batch potency (4 HU).

A peak in viral lung loads was found on D1 post infection. Thus approximately 1000 fold titer reduction in virus load was found in 16 HU and 64 HU (groups 1-2) (lung loads, mean of the right and left lung samples: around 6.6 log $TCID_{50}$/10g lung versus placebo 9.7 log $TCID_{50}$/10g lung). In the 8 HU (group 3) the reduction in lung load was determined to 10 times less i.e. approximately 100 fold (mean of the left and right lung samples 7.6 log $TCID_{50}$/10g lung). However, reduction of viral lung load did not strictly meet the Ph. Eur. criteria for 16 HU on D3 post infection and therefore this does not fully meet the minimum quality criteria for significance according to the Ph. Eur. 963.

The detectable amounts of infectious virus in the nasal swabs were remarkably low in the vaccinated groups as well as in the placebo control group throughout the period monitoring. The remarkable low excretion compared to the high viral lung loads in control animals of this study has not been clarified. It is possible that technical conditions and the human origin challenge strain passaged in cell culture have played a role for the very low amount of detectable infectious virus in the nasal swap samples compared to those measured in the other porcine challenge studies. In these challenge studies excretion of the strain peaked with significantly (around 1000 fold) higher titres.

Therefore, the data from nasal swabs in this challenge study are considered of questionable biological relevance for the use of the vaccine in the field. The data from nasal swabs did not provide further justification concerning choice of minimum potency based on this dose finding study.

Increases in the body temperature started from D1 post challenge with rises to 41 °C for both placebo and all groups of vaccinated animals. A significant difference in body temperatures between vaccinates and controls were not documented.

Data on body weights from the day of challenge to D8 post challenge were presented in later versions of the study report. Pigs vaccinated with batches ranging from 1–64 HU had not lost body

weight at day 8 post challenge, while the unvaccinated group lost body weight. However, the data is based on few animals and a limited period of time without statistical significance.

The protection against severe dyspnoea was not met by the 8 HU (group 3), the original minimum target potency, or in the groups of 4–6 (≤4 HU) with mean dyspnoea scores ≥3 (strong breathing covering the whole body). In groups 1 and 2 (64 and 16 HU) the dyspnoea scores were < 2 (severe abdominal breathing). The control animals had dyspnoea scores of 4 (severe breathing associated with marked movements of the nostrils).

Conclusion

There was an inverse relationship between vaccinated groups (HU content) and the efficacy parameter of viral lung load. The reduction in virus load in 16 HU and 64 HU was found to be approximately 1000 fold whereas in the 8 HU the reduction in lung load was determined to be approximately 10 times less.

The revised minimum vaccine potency of 16 HU is still an acceptable choice of minimum potency from the present study, even though the full Ph. Eur requirements were compromised at Day 3 for reduction in viral load.

A vaccine formulated with ≥16 HU resulted in a reduction in dyspnoea following challenge compared to unvaccinated placebos.

The data for limited detectable nasal excretion of infectious virus in unprotected placebo pigs and vaccinated pigs are of questionable biological relevance for the use of the vaccine in the field.

The study did not support any statistically significant conclusions for body weight and temperature parameters.

The specific serological response showed an overall dose-dependent correlation with the determined HU content of the vaccine.

<u>OOI study 0001/2015</u>

This OOI study included 6 groups, 2 vaccinated groups (32 HU at release and 16 HU at the point of vaccination) and 4 control groups. The vaccine was administered to 13 pigs per group according to the vaccination scheme of RESPIPORC FLUpan H1N1 (1.0 ml twice within 21 days). Seven days after the second administration of the vaccine a challenge trial was conducted. High doses of a heterologous pandemic H1N1 strain originally isolated from pigs in 2014 (FLUAV/sw/Schallern/IDT19989/2014 panH1N1) were administered by aerosol at different infection doses. Four different infection doses were used in order to investigate the influence of dose on the induction of clinical symptoms. The infection strain displayed a low virulence. At the highest dose (9.46 log) overall slight dyspnoea was detectable in placebo-treated pigs. At lower doses almost no symptoms were visible.

In the group corresponding to the duration of immunity study in respect to challenge dose (7.21 log $TCID_{50}/m^3$) a mean maximum score was 0.5 at day 3 morning, while only 2 animals (out of 11) in the experiment had detectable dyspnoea according to the scoring system (scores 1).

The number of animals in the vaccinated and placebo/control groups complies with the minimum 10 animals in each of the groups as stipulated in the Ph. Eur. 0963.

On D7 after primary immunisation all pigs were challenged by aerosol administration of swine origin influenza A virus (H1N1)pdm09 strain (FLUAV/sw/Schallern/IDT19989/2014 (H1N1)pdm09)

(IDT19989). Sequence data of this strain confirms that it is an influenza A/H1N1 pandemic 2009 virus; all segments correspond to A/California/04/2009.

The poor quality of documentation of this study is highlighted in the introductory section. Virus challenge dose was changed by more than 100 fold from 7.53 $\log_{10}$ TCID50/m^3 to 9.46 $\log_{10}$ $TCID_{50}/m^3$ for group 1 and 2 in later versions of the study report. Furthermore, pigs were reported as seropositive in later versions. The parameter investigated was the viral lung load, in later versions of the study report dyspnoea scoring and nasal swap samples for measuring viral load in nasal excretions were added to the study plan and the results were reported.

Information on body weight, rectal temperature and serum antibody levels was provided.

CVMP identified some concerns regarding the serological status of animals used in the study.

Serum VNT titres (VNT titre 204 and 129) were detected before vaccination of two pigs in vaccine group 3 and placebo control group 5. It was also reported that antibodies against influenza A virus infections other than influenza A virus (H1N1)pdm09 have been detected in several sows. It has not been clarified whether the antibodies derive from infections and/or vaccination. This does not comply with Ph. Eur 5.2.7 requiring seronegative animals unless justified to determine the efficacy of a veterinary vaccine.

Significant reduction on viral lung loads in samples of both right and left lung did not strictly meet the Ph. Eur. monograph 0963 criteria. The high viral loads in lungs in this laboratory study in relatively young pigs have been reported to elicit no clinical systemic signs i.e. changes in general health for any of the placebo pigs or vaccinated pigs after challenge. No systemic reactions (score 0, no changes; 1, reduced appetite; 2, sleepiness; 3, apathy) were observed after challenge in any pigs among vaccinated or placebos. Score 0 has been documented for all pigs examined up to D7 after challenge.

The dyspnoea scoring is not considered a valid efficacy parameter as overall only slight dyspnoea was elicited in a few placebo animals in short time frame (comparable to other study where the same challenge strain was used).

The data on nasal excretion was reduced in a narrow time interval on D2 and/or D3 post challenge depending on groups investigated. For the later added groups 3 and 4, which are considered as the relevant groups due to compliance with minimum criteria on reduction in viral lung loads, significant reduction of nasal excretion was identified only on day 3 post challenge. The data on reduction of nasal excretion is only demonstrated for a narrow time interval and therefore of questionable clinical relevance for use in the field.

The new data on body temperature and body weight gains did not reach relevant significance between the vaccinated and placebo-treated group of animals. The results on body weight and rectal temperatures, therefore, did not support any reduction of clinical disease manifestations.

The poor seroconversion rate in the vaccinated animals tested by HI for this specific H1N1pdm09 vaccine has not been clarified. Antibody responses post vaccination for the individual animals (seroconversion) could be in later versions of the study report measured to a larger extent by serum VNT.

Conclusion

The study is difficult to interpret as the potency of the batch used in the OOI study varies between at the time point when it was measured (at release or at the point of vaccination). The 32 HU batch became 16 HU in later versions of the study report and was used to support the minimum potency.

Significant reduction on viral lung loads in samples of both right and left lung was not achieved for D3 in all trials reported in the latest version of the study report. The observed results did not strictly meet the Ph. Eur. 0963 requirements concerning viral lung loads.

The results of dyspnoea scoring of the animals after challenge are not considered sufficient to support any indication relevant for the use of the vaccine on parameters of relevant clinical disease manifestations.

In the absence of other significant clinically relevant data dyspnoea is considered a clinically relevant parameter. The new data on body temperature and body weight gain did not reach relevant significance between the vaccinated and placebo-treated group of animals.

Furthermore, this study cannot be considered acceptable on the basis of issues concerning the presence of neutralising antibodies in some pigs before vaccination. Presence of antibodies at the time of challenge in unvaccinated animals remains unsolved.

Maternally derived antibodies (MDA)

Two reports exist in the dossier to address MDA. One is a summary of a study for which the raw data is not provided and the second study is a laboratory study for which a full report is provided.

A summary of a trial with a maximum potency batch of 64 HU vaccine batch was used to investigate the efficacy of vaccination in the face of maternally derived immunity. The report is of limited value due to the brevity of the summary report.

Vaccination reduced dyspnoea scores for D2 and D4 post challenge, whilst the result on reductions in viral lung loads was not in compliance with the Ph. Eur. 0963. Only a minor reduction in nasal excretion was reported.

The study indicated that MDA has a blocking effect on the detectable HI serum antibody response after vaccination. The benefit of vaccination in the face of the levels of MDA in this trial was at best marginal. The limited protection afforded did not meet the minimum criteria on significant reduction of viral lung loads stipulated in the Ph. Eur. 0963.

In addition, another shortcoming is that the vaccination schedule started at 9–10 weeks of age plus 12–13 weeks of age (therefore 1st vaccination was administered in pigs 1–2 weeks older than minimum age for the intended use) and a vaccine of proposed maximum potency 64 HU was used. This study, did however, provide important information concerning negative interference of maternally derived immunity.

Given the proposed minimum age of 8 weeks, the results reported for study highlighted the importance of investigating the impact of maternally derived immunity on vaccine efficacy further.

Negative interference of maternally derived immunity on vaccine induced protection is strongly indicated from results of this study, and the justification of 56 days as minimum age for vaccination has not been sufficiently documented in pigs with MDA against influenza A virus (H1N1)pdm09.

MDA study

A study was designed to investigate the impact of maternally derived immunity on initial vaccination starting from day 3 of life and repeated 24 days later. The vaccine batch used for vaccination of pregnant sows had a potency of 64 HU at release and 32 HU at time of testing. Sixty (60) piglets, half of them of vaccinated mothers and half of unvaccinated mothers were tested (20 piglets: MDA + vaccination; 20 piglets: MDA without vaccination, 20 piglets: without MDA + vaccination). Nine (9)

days after end of primary vaccination of piglets with a 16 HU dose, a challenge with a human derived strain Influenza A virus/Hamburg/NY1580/2009 (H1N1)pdm09 was conducted.

The challenge strain induced clinical signs especially in placebo-vaccinated piglets.

The data reveals the lack of measurable serological response to vaccination and high viral lung loads in pigs vaccinated in the face of maternally-derived immunity.

Dyspnoea scores were reduced in vaccinated pigs with and without MDA compared to placebo-control animals. There was significant reduction in viral load was found in the group vaccinated without MDA (at day 3 post infection). However, whilst dyspnoea scores were reduced in both vaccinated and in unvaccinated animals with MDA, the results from viral lung loads showed high loads in all 4 groups of pigs.

Conclusion

The studies provided evidence of negative interference by maternally derived immunity.

The applicant's conclusion from the two studies is that a minimal age of 56 days for first vaccination is justified even if there may be still a few pigs with MDA at this time because pigs are better protected after vaccination than unvaccinated pigs.

Notable, the issue on MDA has not been investigated according to the recommended in vaccination schedule in pigs from 56 days of age

DOI study: Duration of immunity over three months after primary immunisation with the vaccine RESPIPORC FLUpan H1N1

The vaccines were administered to 19 pigs in 3 groups according to the vaccination scheme of RESPIPORC FLUpan (1.0 ml twice within 21 days). Two groups of pigs were vaccinated with vaccine batches of 16 HU (group 1) and 8 HU (group 2), respectively. Group 3 was a placebo-control group.

Ninety-two days after the second administration of the vaccine a challenge trial was conducted. High doses of a heterologous pandemic H1N1 strain originally isolated from pigs in 2014 (FLUAV/sw/Schallern/IDT19989/2014 panH1N1) were nebulised. Antibodies were determined. Lungs of the pigs were investigated on day 1 and day 3 after infection for their virus content according to Ph. Eur. 0963. Additionally, clinical symptoms were recorded by measurement of dyspnoea via score. The efficient protection was determined by demonstration of significant differences in the viral lung load of pigs vaccinated in comparison to pigs vaccinated with a placebo.

This study has deficiencies as highlighted in the introduction.

In some sections of the revised study report the two batches are mentioned to be 16 HU or 8 HU. This issue remains unresolved and impacts on the interpretation of the results.

Results

<u>Clinical disease and viral lung load</u>

Dyspnoea was very low in pigs in this 3-month DOI study. The challenge infections elicited hardly any recognisable dyspnoea in only a few of the placebo control animals of the study. The dyspnoea scoring is not considered a valid efficacy parameter for the infection model used in this study.

Reduction for viral lung loads was obtained for the pigs vaccinated with the vaccine batches containing 16 HU; the lung viral loads were reduced by more than 10 fold in the 16 HU groups of pigs

compared to those in the HU 8 group. For both vaccine groups a significant reduction of viral lung loads was demonstrated compared to placebo.

Serology and reduction of nasal virus excretion

There was a short period of detectable HI antibody response after primary vaccination. For group 2 (8 HU) seroconversion rate was 68% and only 9 of the 19 pigs (47%) stayed seropositive for a week. One single pig stayed seropositive in week 4 after primary vaccination.

In group 1 (16 HU) all animals had detectable serum HI antibody levels 7 days after 2nd vaccination (i.e. after ended primary vaccination) (100% seroconversion). The majority of animals stayed seropositive one week later (83%), and 43% were seropositive in week 4 after finished vaccination.

By use of serum VNT antibody responses were detectable in the majority of the vaccinated animals for 3 months after primary vaccination.

The batch of 16 HU exhibited the highest degree of reduction of viral load in nasal excretion (excretion). Virus titers in nasal swabs were significantly lower on days 4-6 after infection and stopped earlier than in the placebo group.

Conclusion

The efficacy study is difficult to interpret given the various versions of the submitted report. Notwithstanding the concerns on the quality of documentation, a statistical significant reduction of viral lung loads was determined, however, the viral lung load is not correlated to any reduction in clinically relevant signs (dyspnoea).

There was a short period of detectable HI antibody response after primary vaccination but by use of serum VNT antibody responses were detectable in the majority of the vaccinated animals for 3 months after primary vaccination.

Virus titers in nasal swabs were significantly lower on days 4–6 after infection and stopped earlier than in the placebo group. If there could be confidence in the determined potency of the batches a reduction of viral lung loads and nasal excretion could be considered acceptable for the 16 HU batch. However, the data are not correlated with a clinically relevant parameter (dyspnoea).

Prevention of transplacental transmission

No studies have been provided. This is considered acceptable.

Additional studies

Studies regarding the association of the two vaccines, RESPIPORC FLUpan (containing H1N1pdm09 subtype) and RESPIPORC FLU3 (containing the subtypes classical avH1N1, huH3N2, huH1N2) have not been performed.

Field studies

Field trials present safety data only, while no efficacy parameters (e.g. virus excretion, dyspnoea, clinical signs) related to the indication of the vaccine were investigated. There was no wild-type virus circulation during the field studies therefore only serological data (seroconversion) was provided.

Field study to test the safety and the efficacy of repeated administration of a single dose

This was a randomised, placebo-controlled GCP study. Group A of 95 pigs were administered RESPIPORC FLUpan H1N1 (16 HU), intermediate potency and Group B of 95 pigs were administered sodium chloride.

The study indicated strong interference to vaccination from maternally derived immunity considering that the seroconversion rate after vaccination was very low compared to data of all presented laboratory studies carried out in seronegative pigs.

Field study to test the safety and efficacy of the repeated administration of a single dose

This was a randomised, placebo-controlled GCP study. Group A of 42 pigs were administered RESPIPORC FLUpan H1N1 (16 HU), intermediate potency and Group B of 42 pigs were administered sodium chloride.

Data presentation was preliminary. Antibody results by use of VNT could indicate three months duration of antibody response after vaccination, notably in pigs with no maternally derived immunity and given that boosting by natural exposure did not take place. No efficacy data against natural exposure and clinical disease in the field was presented.

Field study to test the safety and efficacy of the repeated administration of a single dose

In this field study 160 piglets of 16 gilts of one farrowing group of a German pig farrowing farm was included. At the average age of 45 days the pigs were assigned to one of two blinded groups and were vaccinated twice, at the average age of 45 days and 3 weeks later as follows: group 1, vaccinates: 1 ml of RESPIPORC FLUpan; group 2, controls: 1 ml of physiological sodium chloride solution.

The vaccination schedule of this field study (starting at 45 days of age) was not in line with that of the intended use (day 56), and the potency of the vaccine was not stated.

The results of the investigation revealed that vaccination induces neutralising antibody responses comparable with the DOI laboratory challenge study 0242/2014.

It should be noted that the pigs had no maternally derived immunity. The neutralising antibody responses were detectable in the majority of the vaccinated pigs three months after finished primary immunisation.

Conclusion

Clinical efficacy cannot be evaluated from the presented results from these three field studies. Serum antibody profiles as parameter of protection have not been defined serologically (CVMP Guideline on duration of protection achieved by veterinary vaccines (EMEA/CVMP/682/99), CVMP Guideline on requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs) (EMA/CVMP/IWP/594618/2010)), therefore clinical efficacy in the field cannot be evaluated from the presented results from these three field studies.

Only serological investigations have been conducted; however no correlation between efficacy and threshold of serological parameters has been established. No efficacy against natural exposure and clinical disease in the field has been demonstrated.

Additional information

Report of extended field trials with RESPIPORC FLUpan H1N1

A combination of field study combined with a laboratory challenge to test the efficacy of the repeated administration of a single dose of RESPIPORC FLUpan H1N1, and vaccination of sows (140,605), piglets (26,395) and fatteners/gilts (29,532) in a total of 277 farms with a mean farm size of 535 sows was carried out in Germany.

In the new combined field and experimental challenge study presented in response to outstanding issues (FES04 and 158/16), the aerosol challenge studies involved a swine origin influenza A virus (H1N1)pdm09 virus strain.

A total of 40 pigs were vaccinated with RESPIPORC FLUpan vaccine (16 HU) or placebo vaccine (physiological sodium chloride solution) at an age of between 53-55 days and then 3 weeks later. All pigs vaccinated had detectable levels of serum antibodies measured in HI and VNT against influenza A virus (H1N1)pdm09 subtype. Some pigs exhibit antibodies against other influenza A virus av-H1N1 subtype mostly in group 2 and a few in group 1. Of these vaccinated pigs, 39 pigs were transported a day before challenge to the GLP infection unit. Group 1 included 19 vaccinated pigs and group 2 included 20 placebo control treated pigs.

The experimental challenge was reported to derive with a current field virus isolate originating from a Spanish pig farm in 2016. The challenge with influenza A virus FLUAV/sw/Teo(Spain)/AR641/2016 (H1N1)pdm09 was carried out a week after last vaccination. Differences in the viral lung load of pigs vaccinated in comparison to pigs vaccinated with a placebo were reported. Reduction in nasal excretion measured in viral loads in nasal swaps was reported on days 1 and 3 post challenge. Bodyweight measurements were reported to exhibit significant differences between vaccinated and controls on day 2, 4 and 8 post challenge. Dyspnoea scores were reduced in vaccinated pigs on days 1 and 2 post infection. Temperature measurements on day 1 post infection were reported and some reduction in the vaccinated group compared to the placebo group was documented.

Documentation on propagation of the laboratory challenge virus strain was not provided.

Unresolved issues concerning serological data and on potential exposure of the pigs to influenza A virus av-H1N1 subtype has not been appropriately documented.

The vaccine batch used exhibited a marked drop in potency between Time 0 months (T0) and Time 3 months (T3), declining from 16 HU to 8 HU.

Conclusion of the study

The study could become important concerning the proposed indication on clinically relevant disease manifestations. The study demonstrated a reduction in viral lung load and nasal excretion in vaccinated animals at minimum age using a batch of minimum potency. There was a correlation in reduction in viral lung load and objective clinical parameters. There was a significant difference in dyspnoea, weight gain and body temperature between vaccinated and placebo controls.

Interim Report extended field studies, April 2016

Data of 43 participating farms covering 6 months of vaccination were analysed and compared to the data of a period of 6 months without vaccination. In this report 4 farms where nursery and/or fattening pigs from an age of 56 days were vaccinated, are presented in more detail. Several

different commercial scale batches were used. The potency of the batches used has not been stated (latest version extended field studies, April 2016).

For the evaluation of the efficacy of the vaccine, data regarding mortality rate during nursery and fattening period, performance data such as daily weight gain during nursery and fattening period as well as use of medicines were analysed and compared to data prior to vaccination.

In summary, the data shown (for losses during fattening period a decrease of the mean mortality rate by 0.79% (loss 2.27% for 12 selected farms) for the time of 6 months after vaccination compared to the period of 6 months prior to vaccination (loss 3.06% for 12 selected farms) could maybe indicate that the vaccination of herds (evidence of influenza virus infections not clarified) can improve the general health status and performance of a herd, however such effect would need to be confirmed.

Specifically, laboratory documentation indicating influenza A virus (H1N1)pdm09 infections in the farms included in the reporting has not been reported.

Conclusion

Information concerning simultaneous influenza A virus infections in farms have not been conclusively documented in the report. This missing information makes the data questionable concerning correlation and relevance for actual manifestations related to specific influenza A virus infection of subtype H1N1pdm09 in the monitored farms. This correlation has not been documented.

Overall conclusion on efficacy

The CVMP would highlight from the outset that throughout the procedure the CVMP expressed significant reservations regarding the quality of the documentation submitted by the applicant for the efficacy studies. The applicant also acknowledged the shortcomings in the quality of the three submitted (laboratory) efficacy studies.

Key elements of QA have not been respected.

Therefore reliable conclusions cannot be drawn from these studies concerning efficacy to establish the OOI or DOI. Despite these significant reservations, the CVMP assessed all data available to it and identified significant deficiencies in the efficacy data package: The laboratory studies performed did not provide sufficient evidence of clinically relevant efficacy corresponding to the proposed indications for OOI and DOI when the vaccine was administered in accordance with its intended recommendations for use.

A correlation between a reported viral lung load and viral excretion on one hand and the intended clinical efficacy (reduction of disease manifestations) on the other hand has not been demonstrated in the period from OOI until the end of DOI.

An epidemiologically relevant challenge strain for the necessary evaluation of the benefit of the vaccine in the field has been used in two laboratory studies, however when used did not produce clinically relevant results.

Part 5 – Benefit-risk assessment of the initial application

Introduction

RESPIPORC FLUpan H1N1 is an inactivated monovalent viral vaccine proposed for active

immunisation of pigs against swine influenza caused by subtype (H1N1)pdm09. The active substance of this product is the human origin A/Jena/MSV-VI5258/2009 (H1N1)pdm09 -like virus.

The proposed vaccination scheme for pigs from 8 weeks of age (56 days) is two doses to be given with a 3-week interval between injections. The route of administration is intramuscular use.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

The benefit of RESPIPORC FLUpan H1N1 is intended to consist in active immunisation of pigs from the age of 56 days onwards against swine influenza caused by pandemic influenza A/(H1N1)pdm09 -like viruses to reduce clinical signs, viral lung load and virus excretion after infection.

The efficacy has been investigated in 5 laboratory and 3 field studies. There are, however, significant discrepancies in the design, conduct and reporting of the laboratory challenge studies concerning the dose-finding study and OOI and DOI challenge studies and the report on challenge of pigs vaccinated in the field that affect the interpretation and question the reliability of the results and that prevent conclusions from being drawn on these studies. Therefore, insufficient data have been presented to demonstrate efficacy for the proposed indications.

Sufficient documentation on validation of the potency method remains to be presented. At present it cannot be robustly assured that the potency of the batches used in laboratory settings represent minimum potency batches. This is not acceptable for studies which should document vaccine efficacy at minimum potency.

The laboratory studies performed did not provide sufficient evidence of clinically relevant disease manifestations correlating with the proposed indications when the vaccine was administered as intended.

The biological effect of the documented reduction of the nasal virus excretion shown in the DOI study has not been sufficiently investigated in the field. Potential influence concerning reduction on zoonotic transmission between swine and human has not been clarified by the applicant.

The CVMP, therefore, considers that the data provided are inadequate to provide acceptable evidence of efficacy for the proposed indications, and that the benefit of the product has therefore not been demonstrated.

Additional benefits

None identified.

Risk assessment

Main potential risks have been identified as follows:

Quality:

Information on development, manufacture and control of the active substance and finished product has been partly presented in a satisfactory manner. Quality data provided remain incomplete. Major

outstanding issues remain regarding batch potency and stability of the bulk antigen active ingredient and product. Therefore, the quality of the product remains unsubstantiated and unjustified.

For the target species:

Administration of RESPIPORC FLUpan H1N1 in accordance with the intended use is generally well tolerated in the target animal.

Minor transient local reactions (mostly after second vaccination) and minor transient temperature increases have been observed.

For the user:

The user safety for this product is acceptable when used according to the intended recommendations.

For the environment:

The product is expected to pose a negligible risk for the environment when used according to the intended recommendations.

For the consumer:

Residue studies are not required. The withdrawal period is zero days.

Risk management or mitigation measures

Appropriate information has been identified for inclusion in a summary of product characteristics to inform on the potential risks of this product relevant to the target animal, user, environment and consumer and to provide advice on how to prevent or reduce these risks. Adequate information concerning efficacy and quality are however lacking, which may have require further risk management measures.

Evaluation of the benefit-risk balance

The laboratory and field studies submitted failed to provide reliable results to support the proposed indications in the intended target population likely to be vaccinated with the product. The benefit of RESPIPORC FLUpan H1N1 therefore has not been demonstrated as the efficacy has not been sufficiently demonstrated by data provided by the applicant during the procedure.

The development, manufacture and control of the active substance and finished product of RESPIPORC FLUpan H1N1 is partly presented in a satisfactory manner. However, assessment of the quality of the product remains incomplete as the batch potency testing and the stability of the bulk active ingredients and product has not been satisfactorily described.

Administration of RESPIPORC FLUpan H1N1 in accordance with the intended use is generally well tolerated in the target animal.

On the basis of all data provided, the overall benefit-risk evaluation for the product is negative.

Conclusion on benefit-risk balance of the initial application

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for RESPIPORC FLUpan H1N1 is not approvable since the applicant has not sufficiently demonstrated the

quality and efficacy of the product. Therefore, the data do not satisfy the requirements for the granting of an authorisation as set out in Regulation (EC) No 726/2004 and Directive 2001/82/EC.

The CVMP therefore considers that the overall benefit-risk balance is negative and, a marketing authorisation for the above-mentioned medicinal product cannot be granted.

Grounds for refusal

Whereas

- **Ground for refusal 1 (efficacy):**

  On the basis of all the available data, the CVMP considers that specific documentation provided by the applicant in order to demonstrate the efficacy of the veterinary medicinal product (dose finding and onset of immunity laboratory study; onset of immunity laboratory study001/2015; duration of immunity laboratory study 042/2014) is not reliable.

  Key elements of quality assurance (QA) have not been respected.

  Therefore reliable conclusions cannot be drawn from those studies concerning efficacy. Considering that these studies are a fundamental requirement for the demonstration of efficacy, the deficiency is significant.

  The CVMP reiterates that throughout the procedure it expressed significant reservations regarding such quality of the efficacy documentation submitted by the applicant.

  Despite the significant reservations as identified above regarding the quality of the documentation submitted, the CVMP assessed all data available to it and observed the following deficiencies:

  The laboratory studies performed did not provide sufficient evidence of clinically relevant efficacy corresponding to the proposed indications for OOI and DOI when the vaccine was administered in accordance with intended recommendations for use.

  A correlation between a reported viral lung load and viral excretion on one hand and the intended clinical efficacy (reduction of disease manifestations) on the other hand has not been demonstrated in the period from OOI until the end of DOI.

  An epidemiologically relevant challenge strain for the necessary evaluation of the benefit of the vaccine in the field has been used in two laboratory studies, however, when used did not produce clinically relevant results.

- **Ground for refusal 2 (quality):**

  The validation of the potency test method remains insufficiently demonstrated by the data included in the dossier.

- **Ground for refusal 3 (quality):**

  On the basis of data provided for some of the batches of inactivated/neutralised bulk there is a significant titre decrease during storage. The reasons for this loss in HU content have been investigated and it was found that the decrease in HU content correlates with an increase in pH. It has not been clarified why the pH is increasing during storage for the inactivated antigen bulk, causing the HU content to decrease. The apparent instability of the bulk antigen is of a major concern and cannot guarantee a consistently manufactured and stable active ingredient.

On the basis of the above, the CVMP remains concerned about major outstanding issues in regard to the quality and the efficacy data provided to support the indications.

The CVMP concludes, after verification of all the documents submitted, that the applicant has not sufficiently demonstrated the efficacy and the quality of the veterinary medicinal product.

Therefore, the CVMP recommends by consensus the refusal of the granting of the marketing authorisation for RESPIPORC FLUpan H1N1, in accordance with Article 37(1)(a) of Regulation (EC) No 726/2004.

Re-examination of the CVMP opinion of 8 December 2016

Following the negative CVMP opinion on 8 December 2016 for RESPIPORC FLUpan H1N1, IDT Biologika GmbH requested the re-examination of the CVMP opinion under Article 34(2) of Regulation (EC) 726/2004. At the request from the applicant, an ad-hoc expert group (AHEG) meeting was held on 6 March 2017, which was also attended by the applicant.

The applicant's grounds for re-examination, the AHEG's responses to the questions by CVMP and the CVMP final conclusions are given below.

Ground for re-examination 1 (reliability of efficacy documentation)

The applicant acknowledged the shortcomings of the efficacy documentation initially presented in the application for the marketing authorisation of RESPIPORC FLUpan H1N1 that led to the reliability of the documentation being questioned by the CVMP. However the applicant believes that systematic processes to rectify data inconsistencies and to provide all missing data were addressed in response to the questions from CVMP and resulted in the provision of amended and reliable study reports that allow efficacy assessment of RESPIPORC FLUpan H1N1.

The applicant states that the animal phases of the four efficacy studies were conducted in accordance with GCP in a GLP test facility and in accordance with approved protocols. However, the data handling from raw data into reports was poorly conducted. As quality assurance of the study report failed as well, due to efficacy studies not being required to be audited in a GLP quality assurance system, this deficiency was not detected.

Investigations were undertaken to check both data entry and data analysis in its entirety. The internal investigation concluded that entry of raw data of studies was not performed according to the procedures established. Data entry was corrected and an external company checked it. As a consequence statistical evaluations had to be re-done and graphs had to be newly generated. According to the applicant's view this correction did not lead to a change of the overall study conclusions.

Not all of the data generated in the course of the efficacy studies were included in the reports initially submitted. These data were included in the amended study reports that were submitted in response to the list of outstanding issues.

In the amended study reports of studies extra groups of animals were included. These additional study groups were part of the protocol and included for scientific purposes with the objective to reduce the number of animals used by avoiding repeated use of treatment groups. It is the opinion of the applicant that the missing data have no impact on the overall efficacy assessment of the vaccine.

With regard to blinding, it is stated that the studies were blinded for clinical assessment on a group level (i.e. the investigator was aware of which animal belonged to which group) but unaware of the treatment given to the respective groups, which was a necessary measure allowing the investigator to control that the correct number of animals per treatment group was selected for viral lung load determination at day 1 and day 3. Thus, the applicant does not agree with the Committee that blinding of the study groups was not performed.

The challenge was performed as described in the respective reports and further explained in the course of the procedure. All animals were located in the same challenge room and exposed to the

same challenge dose. The procedure of aerosol infection was accepted earlier in the procedure. The primary efficacy endpoint was chosen in line with the Ph. Eur. monograph 0963 and remained unchanged except in one study report (viral load data of the left and right lung lobe were assessed combined instead of separately). Statistical analysis of secondary efficacy parameters (e.g. dyspnoea, viral load in nasal swabs) as well as supportive parameters (e.g. body weight and rectal temperature) was performed per study day. The secondary efficacy parameters have remained unchanged in the efficacy reports and do allow conclusions on the efficacy of the vaccine.

Initially, the statistical analysis was performed by the project leader. It was decided during the licensing procedure to have the statistical evaluation reviewed by an independent company. The statistical methods originally used were found to be appropriate and only one correction was required. The p-values for the viral load in the lung were originally claimed to be calculated with a one-sided test but were in fact calculated with a 2-sided test. This error was corrected during the licensing procedure and is also corrected in the revised and amended study reports. The overall results from the study reports were not affected by the single correction in the statistical evaluation.

Other changes in the study reports were explained as follows:

Change of study title and study plan*:* The titles were corrected to those of the related protocols. The schedules of events were amended because it was noted during the quality assurance audit that the ones of the reports were not in line with those of the study protocols. Missing information about time points of measurement of rectal temperature and body weight were added. It is emphasised that the study plans remained unchanged and that changes made in the schedule of events were related to non-essential parameters (i.e. measurement of rectal temperature and body weight) that did not change the overall conclusion about the efficacy of the vaccine.

Change of vaccine potencies: The reported vaccine potencies of two vaccine batches and one "research" batch were changed in the amended study reports. This is because the potencies of batches were reported as they were at time of release and it had not been taken into consideration that the titres had decreased by one $\log_2$ by the time the study started. For the research batch the potency one month before start of the study (time of study protocol generation) was reported but the potency which was measured 10 and 17 days after start of the study was considered more relevant.

On the basis of the above points, the applicant disagrees that the amended reports do not allow conclusions about the efficacy of the vaccine because the quality deficiencies in the data analysis and reporting of the studies were clearly identified and could be fully addressed. The 100% review of all raw data by a third party could restore the reliability in the data and the revised and amended study reports. Despite all the shortcomings and deficiencies, the applicant is convinced that the efficacy data for the efficacy assessment and the overall conclusions on the efficacy of the product remain valid.

The AHEG were asked whether they considered the revised reports complete, in line with the respective protocols and a reliable representation of the performance of the studies and the raw data generated.

The experts considered that the documentation still had deficiencies and errors, which undermine the group's confidence on the data. It also makes the data difficult to interpret when there are still inconsistencies in the re-submitted data. The inconsistencies in the documentation led to the perception of lack of reliability of the data presented.

The CVMP recognised that, as noted by the AHEG, there were still some discrepancies and errors in the reports. However, the CVMP also noted that the revised reports are, with a few exceptions,

consistent with the respective protocols. The discrepancies were relatively minor and are unlikely to have affected the conclusions reached. For example, in the case of the specific example quoted by the AHEG it had been intended to compare each of the vaccinated groups (1 and 3) in study TV with separate placebo groups (2 and 4 respectively) whereas it is suggested in the description of the statistical analysis that both may have been compared with the same placebo group (group 3). In fact, the statistics summary clearly indicates that both vaccinated groups (1 and 3) were correctly compared with their respective placebo groups (i.e. group 1 with group 2 and group 3 with group 4) and therefore the discrepancy referred to was considered a typographical error. Another discrepancy between the revised report and the study protocol was that according to the protocol study was originally intended to include an additional group (group 8 in the protocol) vaccinated with RESPIPORC Flu3 that is not mentioned in the final report. The absence of this group did not impact on the purpose and conclusions of the study, but this deviation from the protocol should have been documented in the report. There were several other minor deviations from the protocols that are documented in the reports and are unlikely to have affected the outcome of the studies. It was therefore concluded by CMVP that the reports could be accepted as a valid description of the efficacy studies as carried out.

Conclusions on grounds for re-examination 1:

The CVMP concluded that, whilst there are still some minor discrepancies between the protocols and the study reports, these have not affected the outcome of the efficacy studies and agreed that the final, audited versions of the study reports submitted are reliable reports of the studies conducted.

Ground for re-examination 2 (clinical relevance of the efficacy data)

The efficacy parameters assessed were 3-fold:

1. measurement of viral lung load 1 and 3 days post infection (in line with Ph. Eur. 0963);
2. measurement of viral load in nasal secretions; and
3. assessment of dyspnoea (based on a pre-defined scoring system).

In all studies vaccination was performed with RESPIPORC FLUpan H1N1 containing a minimum potency (16 HU) in the minimum age piglets.

The applicant believes that the laboratory studies performed provide sufficient evidence of clinically relevant efficacy because:

- A significant reduction of viral lung load is known to correlate with reduction of clinical disease (Richt et al, 2013, van Reeth et al, 2001), thus a reduction of viral lung load (i.e. reduction of infection) alone is already indicative for a benefit of the vaccine in the field.
- A significant and relevant reduction of viral load in the lung and nasal excretions could be seen in all studies.

  All batches of vaccine that contained a minimum of 16 HU/dose clearly reduced the viral burden in the lungs and on average a 480 fold reduction in viral lung load were achieved across the studies, which are clearly relevant from the clinical perspective. In fact disease severity with influenza viruses is strongly dependent upon virus replication levels and even a small reduction of virus replication can avoid disease (van Reeth et al 2001). It is important to note that in the three OOI studies the challenge was given one week after the last administration of the vaccine

whereas Ph. Eur. monograph 0963 indicates to perform the challenge infection three weeks after the last administration of the vaccine. This has made the demonstration of a relevant and significant reduction of the viral lung load even more demanding.

The endpoint for this efficacy parameter is the area under the curve of viral excretion (AUC, viral excretion over time) as this covers both the extent and the duration of the viral excretion. The reduction of this total virus excretion is relevant for both the animals and the environment because the viral replication rate in the lung correlates with the infectious dose. This implies that a reduced excretion of influenza virus (challenge exposure) will also result in reduced infection in the lung and thus in a reduced severity of clinical disease in other pigs. Considering the zoonotic potential of this influenza subtype, the reduced excretion has as well a benefit for potential infection in humans.

In young animals (OOI studies) the peak of viral excretion occurs during the first days after the challenge infection. The area under the curve (AUC) of viral excretion was calculated over the first 3 days after the challenge infection when still a sufficient number of animals (i.e. 7–14 animals) were available for this type of calculation and this measure was consistently applied across the studies. The reduction of nasal virus excretion was 250 fold in case of the challenge strain of human origin and ≥ 4000 fold in case of the challenge strains of swine origin. In all three OOI studies the reduction of virus excretion was highly significant and clinically relevant for both the animal and the (porcine and human) environment.

In the DOI study (animals older at point of challenge) the peak of viral excretion occurred around 5 days post challenge. In this study the cumulative reduction over these 9 days was 500 billion fold and again highly significant ($p=0.002$).

The results are considered of clinical relevance as a reduction of nasal excretion is known to correlate with a reduced transmission rate (Romagosa et al, 2011) and has been found to correlate with a reduced replication rate in other pigs.

- A significant and relevant reduction of dyspnoea could be seen in all studies even though the severity of dyspnoea differed per challenge strain.

The relevance and suitability of the challenge strains used have also been addressed. The following points are considered:

- All H1N1pan viruses are highly comparable in terms of genetic and antigenic properties (Su et al, 2015) and therefore all challenge strains that were used can be considered epidemiologically relevant and comparable in terms of their antigenic properties. All of the challenge strains used for the evaluation of the efficacy of this vaccine in swine are epidemiologically relevant because the antigenic and genetic properties of human and swine derived H1N1pan influenza strains used are highly similar (i.e. no genetic or antigenic differentiation between H1N1pan influenza strains derived from humans or swine can be made). As a result all challenge strains used can be considered epidemiologically relevant and comparable in terms of their antigenic properties. If efficacy of RESPIPORC FLUpan H1N1 can be shown against one H1N1pan isolate it is therefore reasonable to infer that it will also protect against other H1N1pan isolates. This was proven by the use of three different challenge strains and demonstration of a significant reduction of viral load and dyspnoea for all three challenge strains.
- Reproduction of typical flu symptoms by experimental inoculation is difficult and may vary from strain to strain. For that reason and because of the significant correlation between lung virus titres and clinical manifestation of the disease the reproduction of typical flu symptoms has thus

been omitted for the revised Ph. Eur. monograph in 2003 (Richt et al. 2013). The three challenge strains used to demonstrate the efficacy of the vaccine all caused clinically relevant disease in the challenged control animals, i.e. high viral loads in lung and nasal excretions, loss in body weight and dyspnoea. In all cases, the challenge administered was valid since all placebo animals were shown to have been infected by the challenge virus.

- A significant reduction of dyspnoea could be shown in all four efficacy studies even though the severity of dyspnoea in control animals differed per challenge strain. Thus, independent from the severity of dyspnoea a significant and relevant reduction of dyspnoea was always observed.
- In the two studies in which the challenge strain FLUAV/sw/Schallern/IDT19989/2014 was used the severity of dyspnoea varied among animals, but still more animals in the control group than in the vaccinated group developed moderate cumulative dyspnoea scores.
- Detailed information from the extended use in the field trial was provided for 4 of the farms where the presence of H1N1pan was confirmed by serology and/or virus detection in nasal swabs shortly before the start of vaccination. Data on weight gain, mortality and antibiotic use over the 6 months periods before and after the vaccination demonstrated a beneficial effect.
- Even though clinical relevance of all challenge strains was shown it should be noted that many marketing authorisations of vaccines are based on the claim “reduction of infection”, i.e. the reduction of clinical disease is not mandatory for receiving a marketing authorisation. Considering that RESPIPORC FLUpan H1N1 has a high safety profile and would be the first pandemic H1N1 in swine, the vaccine (even without the claim “reduction of dyspnoea”) would still be an important tool in combatting this virus in the swine population.

In conclusion, the applicant is of the opinion that the data generated in the laboratory efficacy studies (OOI and DOI), the combined laboratory/field efficacy study (OOI) and in the extended use in the field together have sufficiently demonstrated the correlation between reported viral lung load and viral excretion on one hand and the intended clinical efficacy (reduction of disease manifestations) on the other hand in the period from OOI until the end of DOI. It should be noted that many marketing authorisations of vaccines are based on the claim “reduction of infection”, i.e. the demonstration of a correlation between viral load and clinical efficacy appears not to be absolutely mandatory for receiving a marketing authorisation and can thus not be a ground for refusal. Considering that RESPIPORC FLUpan H1N1 has a high safety profile and would be the first pandemic H1N1 in swine, the benefits as shown under extended use in the field outweigh the potential risks.

The AHEG was asked to consider whether the efficacy data provided by the applicant is sufficiently scientifically robust to demonstrate that RESPIPORC FLUpan H1N1 when administered to pigs is effective in immunisation against swine influenza caused by pandemic subtype H1N1 to reduce clinical signs (dyspnoea), viral lung load and viral excretion after infection. The following should be considered:

a) designs of studies to characterise dosage, onset of immunity and duration of immunity,

b) whether test population and the conditions under which the studies were conducted are representative of the target population and challenge in the field,

c) sample size,

d) the approach to efficacy assessment, including the choice of primary efficacy endpoints and the interpretation of efficacy parameters and whether they correlated to the clinical disease situation,

e) final statistical analysis, and

f) challenge strains used and their clinical relevance in relation to epidemiology of the disease in the EU.

There was no agreement within the experts on whether the designs of studies were appropriate. Some members accepted them as appropriate but they all agreed on the following shortcomings.

The studies are not completely performed in compliance with the Ph. Eur. monograph as the time between vaccination and challenge was 7 days instead of 21 days as indicated in the monograph. In the control groups of one study antibodies could be detected at the time of vaccination.

The animals for the immunogenicity tests were appropriate. However, the animals used in the field study showed MDAs. This compromises part of the evaluation of the study.

The sample size used was considered in accordance with relevant Ph. Eur. monograph.

Regarding the choice of primary efficacy endpoints (viral lung load and viral excretion) and the interpretation of efficacy parameters, endpoints are considered appropriate but not all the claims have been demonstrated. There is clear reduction in viral load in the lungs but less certainty around reduction in virus excretion and clinical signs. There might not be strict correlation between the reduction in viral load in the lungs and reduction of dyspnoea.

Even though the group felt they do not have enough expertise on statistics they feel there is no consistency in the statistical analysis. It seems like that there was a selective presentation of statistical analysis related with nasal shedding and clinical signs.

Relevance of strains to currently circulating ones may be questioned. No documentation is provided in this regard. However, it is acknowledged that the target strain of the indication is a California–like strain.

At the time the strains were chosen they were adequate.

The CVMP recognised that no efficacy studies had been carried out with challenge at the time point indicated in Ph. Eur. monograph (21 days) but also noted that studies had been carried out with challenge at an earlier time point (7 days) and also at a later time point (92 days). The CVMP considered that this was an acceptable deviation from the Ph. Eur. monograph.

The neutralising antibodies present in some animals at the start of study, as noted by the AHEG, were most likely maternally derived since the applicant had indicated that all of the affected pigs were the offspring of the same seropositive sow. As explained by the applicant, these animals were not excluded because their responses were similar to other animals in the groups and the presence of these antibodies would only have been expected to make the results less favourable for the vaccine.

The CVMP accepted the view of the AHEG that the animals for the immunogenicity tests were appropriate, that the sample size used was in accordance with the relevant Ph. Eur. monograph and that the choice of primary efficacy endpoints (viral lung load and viral excretion) and the interpretation of efficacy parameters and endpoints were considered appropriate. There was a clear reduction in viral load in the lungs and therefore this indication could be accepted. The results for reduction of viral excretion and dyspnoea were less clear cut but significant reductions were noted at some time points. With respect to viral excretion, the CVMP considers that a significant reduction in viral excretion was demonstrated in studies . The CVMP considers that while a claim for a reduction in dyspnoea is supported at onset of immunity, it has not been demonstrated at duration of immunity (because a different challenge strain was used which supported a reduction of viral lung load and

viral excretion but did not induce marked dyspnoea). Nevertheless, given that a reduction in dyspnoea could be demonstrated with two of the three challenge strains used, this provides support for the clinical relevance of the vaccine.

While the field studies were compromised by the presence of MDA, the difficulty in carrying out satisfactory field trials for this type of vaccine and the uncertainty of a natural field infection occurring during the trial were recognised. One trial had been carried out by experimental challenge of animals that had been vaccinated in the field to demonstrate that such animals could be protected by the vaccine. In addition, the applicant has not proposed any claims for the vaccine on the basis of the extended field trials.

With regard to the challenge strains chosen, the CVMP noted the agreement of the AHEG that the strains were satisfactory at the time the studies were carried out. However, notwithstanding this point, it should be highlighted that three challenge strains in total have been used to demonstrate the efficacy of RESPIPORC FLUpan H1N1, including one recent isolate from 2016. The CVMP noted that the AHEG were of the opinion that there is a significant unmet need at present for a pandemic H1N1 virus vaccine in the EU.

Conclusions on grounds for re-examination 2:

The CVMP concluded that the design of the efficacy studies was in compliance and met the criteria in the Ph. Eur. monograph and the endpoints chosen were adequate to demonstrate efficacy. The results from the studies supported the claims of reduction of viral load in the lungs and reduction of viral excretion at 7 days and 3 months post-vaccination when animals were challenged with strains clinically relevant to the epidemiology of the disease in the field. In support of the clinical relevance of the vaccine, a reduction in dyspnoea was also demonstrated with two of the three challenge strains used in the efficacy studies, however this was not demonstrated at three months post-vaccination due to use of a challenge strain which did not induce severe clinical signs. The CVMP considered that the benefits of vaccination support the claims of reduction of viral load in the lungs and reduction of viral excretion and will allow use of the vaccine according to a risk-benefit assessment based on the epidemiological situation in a particular EU Member State.

Ground for re-examination 3 (robustness of quality data)

Validation of the potency test

The applicant considers that the hemagglutinin (HA) potency test as initially submitted has been fully validated in accordance with VICH GL 1 and 2 and that the test has a high precision and accuracy (i.e. ability to discriminate between potent and sub-potent batches) which is equal or better than the potency test as described in the Ph. Eur. monograph 0963 (Porcine influenza vaccine (inactivated)). Both the increase of the minimum potency (to 16 HU) as well as the introduction of a minimum release limit (32 HU) are unrelated to the potency test performance in itself.

Multiple samples from the same homogenous samples over a period of time were tested to show that the HA assay has a good level of precision. The data are well suitable to confirm the precision of the HA assay. The long time-interval for testing the multiple samples from the same homogenous sample can be seen as a worst case situation. As there is a good precision over a longer period of time, the precision over a shorter period of time will certainly be good.

The data provided showed that the intermediate precision of the HA assay is more than adequate from 16 HU onwards (the minimum specification). The variation seen for batches with as starting

potency of 8 HU or 4 HU is not relevant in the context of the current specifications for the product (16 HU). Furthermore the assay is able to detect a 2-fold difference in antigen content. In this respect it is superior to the in vivo test using guinea pigs indicated in Ph. Eur. monograph 0963.

The use of an in vitro method is also in line with the 3Rs concept. However, in the view of the applicant, this should not automatically lead to stronger assessment criteria with regard to the precision of the in vitro assays, their ability to discriminate between potent and sub-potent batches (accuracy) and the evaluation of stability data. The in vitro test may show some decrease in potency over time which would never had been observed by the less accurate in vivo potency tests with serology and even less by in vivo potency tests followed by challenge.

The applicant considers that the increase of the minimum potency from 8 HU to 16 HU and the introduction of a minimum release limit are unrelated to the potency test performance itself. The minimum potency was increased because batches with a potency of 16 HU showed better efficacy than batches with a potency of 8 HU. It is important to notice that the upper release limit (64 HU) as well as all other release specifications have remained unchanged during the whole course of the procedure. In order to ensure stability of the vaccine until the end of shelf life a minimum release limit was introduced. The minimum release limit was initially 16 HU but in the course of the increase of the minimum potency from 8 HU to 16HU, the minimum release limit was increased from 16 HU to 32 HU.

The AHEG was requested to advise on whether the potency test and the proposed release limit of at least 32 HU, including repeated measurements, so that 2 out of 3 must be at least 32 HU, are fit for purpose to ensure that only vaccines batches of adequate efficacy would be released into the market.

The experts are of the opinion that the company has shown some correlation between the potency measured and the clinical effects. The test is reasonably robust in terms of repeatability.

It was acknowledged that the potency test method selected is no longer in use in vaccines for human use.

With the data provided it is accepted that sub-potent batches can be identified.

The CVMP noted that the AHEG considered that the potency test had been satisfactorily validated and that sub-potent batches could be identified, although it was also pointed out that this old test method was no longer used for vaccines for human use.

As the efficacy of batches with a potency of 8 HU/dose (i.e. 50% of minimum efficacious titre of 16 HU/dose) has been demonstrated in challenge studies in the target species, the CVMP considered that the potency test and the revised minimum release limit of 32 HU/dose were suitable to ensure that only efficacious batches would be released to the market and therefore is fit for purpose.

Stability of the finished product

The applicant is of the opinion that the stability data generated for the finished product are suitable to support a shelf life of 15 months. Stability data for seven batches have been generated. Five batches were released with a potency of 16 HU, two batches were released with a potency of 32 HU. All batches have been stored at 2–8 °C. Over time, the potency of the batches showed a drop from 16 to 8 HU or from 32 to 16 HU, i.e. one $\log_2$ step in the HA titration. This means that the potency dropped from 100% (value at release) to a value between 100% and 50%, but never lower than 50% after storage of up to 27 months and for one batch for up to 36 months.

According to the applicant, the stability data provided for the 3 consistency batches which were blended at 16 HU support a shelf life of 24 months (27 months available). Data has also been

provided for batches blended at the increased minimum release limit (32 HU), and the potency results seen with the 32 HU batches are consistent with the 16 HU batches. Taken together, the applicant considers that this complete set of data supports a shelf-life of at least 15 months for the finished product (since one of the batches remained within the potency specification at 18 months and another batch is satisfactory at 36 months). Stability studies are ongoing for one of the batches (blended at 32 HU at release) and the applicant commits to undertake stability studies with two additional batches blended at a minimum release titre of 32 HU. The competent authorities will be notified immediately should non-compliance issues occur.

The AHEG was requested to consider whether the data provided are sufficient to support the applicant's proposed 15 month shelf life taking into account that three batches released at 16 HU/dose showed a decrease of 1 $\log_2$ in potency over a 27 month test period and that two batches released at 32 HU/dose showed a decrease of 1 $\log_2$ in potency over 36 months (1 batch) and 18 months (1 batch).

The AHEG considered that a shelf-life for the vaccine of 15 months is not supported. Extrapolation of stability data obtained with batches of 16 HU is not considered appropriate. The group cannot recommend any shelf-life period for the vaccine based on the data provided.

Although the AHEG considered that extrapolation of stability data was not appropriate, the CVMP noted the decrease in potency for batches released at 32 HU/dose was of the same order as that for batches released at 16 HU (i.e. no more than 1 $\log_2$ decrease in potency during 18 months storage for 1 batch and 36 months storage for a second batch). While the full complement of stability tests has only been performed for one of the batches released at 32 HU/dose (i.e. the batch tested to 18 months to date), the applicant has agreed to carry out studies with additional batches of 32 HU/dose. Considering this, the CVMP agreed that a shelf life of 12 months is acceptable.

Stability of the bulk antigens

The applicant does not wholly agree with the statement "the bulk antigen is apparently unstable", and that "stability of the active ingredient cannot be guaranteed". It was found that for two isolated batches which were released the higher end of the pH specification, the inactivated antigen was found to be less stable. An investigation into the apparent instability of the antigen has revealed that by adjusting the pH at the end of the inactivation and neutralisation process the lower end of the pH specification consistent and stable batches of the active ingredient can be guaranteed over the proposed storage period.

The applicant is of the opinion that the production of stable antigen bulk can be guaranteed by controlling the pH more tightly prior to storage and this should not be a ground for refusal because:

- By adjusting the pH to the lower end following inactivation and neutralization the antigen bulk remains stable over a period of at least 5 months.
- The applicant intends to measure the pH and antigenic content of any new antigen bulk prior to blending and any antigen bulk outside the current specification will not be used for blending of final product.

It is therefore proposed to introduce tighter pH limit at the release of the antigen bulk to ensure stability of the antigen bulk during storage and to apply a 5 months shelf life for antigen bulk based on the data to date.

Given the explanations from the applicant the AHEG was asked to consider whether the increase in pH observed during storage of the inactivated antigen bulk is adequately explained and acceptable

and also to indicate whether they agree with the proposal that storing the bulk antigens for a maximum of 5 months under the conditions indicated (i.e. adjusting the pH following inactivation and neutralisation and to measure the pH and antigenic content of any new antigen bulk prior to blending) will enable the production of vaccine batches that consistently meet the required specification throughout the shelf life.

The AHEG concluded that the increase in pH observed during storage of the inactivated antigen bulk was not explained by the applicant.

Data for only 2 batches of bulk antigens were provided but are not considered sufficient to draw conclusions.

The CVMP accepted the AHEG's view that the increase in pH observed during storage of the inactivated antigen bulk was not explained by the applicant and that data for only 2 batches of bulk antigens for which the pH had been adjusted the lower end of the specification following inactivation and neutralisation were not sufficient to draw conclusions. However, the CVMP noted the preliminary data indicated no drop in potency and only a minor increase in pH over a 5 month storage period for antigen batches adjusted to the lower end of the specification following inactivation (i.e. pH increase to a maximum of 7.5).

The applicant's proposal to restrict the storage period of the antigen to 5 months and to measure the pH and antigenic content of any new antigen bulk prior to blending was considered reasonable and provided some assurance that only satisfactory antigen bulks would be used for antigen blending. Any antigen bulk that did not meet the required specification would have to be discarded. This minimises the risk of using unstable antigen batches in vaccine blending. Further stability data were required but on the basis of the above consideration it is accepted that antigen bulks could be stored for up to 5 months before blending.

Conclusions on grounds for re-examination 3:

The CVMP concluded that the potency test has been adequately validated and is fit for purpose to ensure that only efficacious batches would be released to the market. Furthermore, the test represented an in vitro alternative to the in vivo potency test stated in Ph. Eur, which is welcomed from a 3Rs perspective.

Although the CVMP noted that the increase in pH observed during storage of the inactivated antigen bulk had not been adequately explained, it was agreed that the proposal to restrict the storage period of the antigen to 5 months and to measure the pH and antigenic content of any new antigen bulk prior to blending is acceptable.

Regarding the stability of the final product, the CVMP agreed that based on the available data a shelf life of 12 months is acceptable.

The applicant is recommended to provide the following information post-authorisation:

- Stability data for at least an additional batch of antigen bulk
- Stability data for at least 2 additional batches of vaccine released at the proposed specifications and including full set of stability tests.

Overall assessment and conclusions on grounds for re-examination

The CVMP concluded that the final, audited versions of the study reports submitted are reliable reports of the efficacy studies conducted, which were in compliance with the Ph. Eur. monograph and

that the endpoints chosen were adequate to demonstrate efficacy. The results from the studies supported the claims of reduction of viral load in the lungs and reduction of viral excretion at 7 days and 3 months post-vaccination when animals were challenged with strains clinically relevant to the epidemiology of the disease in the field.

The CVMP concluded that the potency test has been adequately validated and is fit for purpose to ensure that only efficacious batches would be released to the market.

The CVMP agreed that the proposal to restrict the storage period of the antigen to 5 months and to measure the pH and antigenic content of any new antigen bulk prior to blending is acceptable.

Regarding the stability of the final product, the CVMP agreed that based on the available data a shelf life of 12 months is acceptable.

Final benefit-risk assessment

Introduction

RESPIPORC FLUpan H1N1 is an inactivated monovalent viral vaccine proposed for active immunisation of pigs against swine influenza caused by subtype (H1N1)pdm09. The active substance of this product is the human origin A/Jena/MSV-VI5258/2009 (H1N1)pdm09 -like virus.

The proposed vaccination scheme for pigs from 8 weeks of age (56 days) is two doses to be given with a 3-week interval between injections. The route of administration is intramuscular use.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

RESPIPORC FLUpan H1N1 was shown to induce active immunisation of pigs from the age of 56 days onwards against swine influenza caused by pandemic influenza A/(H1N1)pdm09 -like viruses to reduce viral lung load and virus excretion after infection.

The efficacy has been investigated in 3 laboratory studies and one combined field/laboratory study. Onset of immunity has been established at 7 days and duration of immunity has been shown to persist for 3 months.

Reduction of dyspnoea caused by pandemic influenza A/(H1N1)pdm09 -like viruses was also demonstrated during the efficacy studies conducted to determine onset of immunity and this further supports the clinical relevance of vaccination. However, given that this efficacy parameter was demonstrated robustly only for the onset of immunity studies (and not the duration of immunity study), it was considered insufficiently supported as an indication for use.

Additional benefits

RESPIPORC FLUpan H1N1 has been shown to have an acceptable safety profile and an indication of reduction on antibiotic use was observed in H1N1 positive farms post vaccination during the field trials.

There is currently no authorised vaccine for immunisation of pigs against pandemic flu and would therefore fill a gap in the EU market.

The reduction of viral excretion is a relevant claim because of the zoonotic nature of this infection.

Risk assessment

Main potential risks have been identified as follows:

Quality:

An increase in pH has been observed during storage of the inactivated antigen bulk that can affect the stability over time.

Full stability tests have only been performed for one batch released at the proposed potency and only a shelf life of 12 months can be accepted.

Safety:

Risks for the target animal:

Administration of RESPIPORC FLUpan H1N1 in accordance with SPC recommendations is generally well tolerated.

Minor transient local reactions (mostly after second vaccination) and minor transient temperature increases have been observed.

The safety of the vaccine has not been evaluated during pregnancy or lactation.

Risks for the user:

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment:

The product is expected to pose a negligible risk for the environment when used according to the SPC recommendations.

Risk for the consumer:

Residue studies are not required. The withdrawal period is zero days.

Risk management or mitigation measures

Appropriate information has been identified for inclusion in a summary of product characteristics to inform on the potential risks of this product relevant to the target animal, user, environment and consumer and to provide advice on how to prevent or reduce these risks.

It has been shown that the presence of maternally derived antibodies in piglets interferes with the response to vaccination and a suitable warning has been included in the SPC to mitigate this risk.

As the safety of the vaccine has not been evaluated during lactation or pregnancy a warning has been included in the SPC to mitigate the risk.

The storage period of the inactivated antigen bulk has been reduced to 5 months and appropriate testing will be performed on each bulk to ensure that only batches of acceptable stability are used in vaccine blending.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious in the reduction of viral lung load and virus excretion after infection with pandemic influenza A/(H1N1)pdm09 -like viruses.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have satisfactory and uniform performance in clinical use.

Administration of RESPIPORC FLUpan H1N1 in accordance with the intended use is well tolerated by the target animals and do not pose any relevant risk to users, environment and consumers when used as recommended.

Appropriate precautionary measures have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy in the application for marketing authorisation, the applicant's detailed grounds for the re-examination, the report to the CVMP from the Ad Hoc Expert Group meeting, and the oral explanations provided by the applicant, the CVMP concluded by majority decision that the application for RESPIPORC FLUpan H1N1 is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore recommends the granting of the marketing authorisation for the above mentioned medicinal product.

Divergent position on a CVMP opinion on the granting of a marketing authorisation of RESPIPORC FLUpan H1N1 (EMEA/V/C/003993/0000) following the re-examination

The undersigned have a divergent position to the CVMP opinion on this application for a marketing authorisation, for the reasons outlined below:

The specific documentation provided by the applicant in order to demonstrate the efficacy of the veterinary medicinal product (dose finding and onset of immunity laboratory study; onset of immunity laboratory study; duration of immunity laboratory study) is still not considered reliable.

Key elements of quality assurance have initially not been respected including e.g. numerous revisions to some study reports leading to changes in critical information including e.g. study plan with introduction of additional groups; repeated errors of reporting results in tabular form; groups were not blinded for clinical assessment; complete and essential data were not provided; efficacy endpoints (viral load, viral excretion, dyspnoea) were incomplete and subject to variation; different approach for the statistics; the change of the vaccine potencies used in the studies at different time point during the evaluation process.

The applicant acknowledged in his response of October 2016 to the list of outstanding issues that the study reports which were submitted to the authorities did not meet the internal quality standards requirements (page 26/60). He indicated (page 27/60) that measures were taken with regard to some employees, that he asked for a complete data check of all efficacy reports by the Quality control department of an external company to be performed, and that he asked for the statistical methods and calculations made in the different reports to be reviewed by an independent statistician of the same external company. Furthermore, the quality assurance department of the same external company was ordered to perform an audit of protocols and reports on the three efficacy reports in order to verify collection, recording and reporting of data, to further verify that the analysis of the data was conducted in compliance with the study protocol and to finally verify that the results incorporated in the final study report accurately reflect the raw data produced during the study. This audit has led to a number of shortcomings, making it necessary to amend the study reports. Finally, in order to guarantee that this obvious lack of quality of efficacy reports will not happen again, further corrective actions were undertaken.

Now, several corrective measures were undertaken by the applicant, but no inspector of any EU competent authority was commissioned to verify that the corrective measures taken were sufficient and accurate to make the current dossier reliable.

Therefore reliable conclusions cannot be drawn from those studies concerning efficacy. Considering that these studies are a fundamental requirement for the demonstration of efficacy, the deficiency is significant.

Despite the significant reservations as identified above regarding the quality of the documentation submitted, the following efficacy deficiencies were observed:

The laboratory studies performed did not provide sufficient evidence of clinically relevant efficacy

corresponding to the proposed indications for onset of immunity (OOI) and duration of immunity (DOI) when the vaccine was administered in accordance with intended recommendations for use.

A correlation between a reported viral lung load and viral excretion on one hand and the intended clinical efficacy (reduction of disease manifestations) on the other hand has not been demonstrated in the period from OOI until the end of DOI.

An epidemiologically relevant challenge strain for the necessary evaluation of the benefit of the vaccine in the field has been used in two laboratory studies, however, when used did not produce clinically relevant results.

It is thus considered that the benefit-risk ratio of the product is negative.

London, 16 March 2017

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