# Annex IV

# Scientific conclusions and grounds for amendment of the summary of product characteristics and package leaflet

# Overall summary of the scientific evaluation of Suvaxyn PRRS MLV

## 1. Introduction

Suvaxyn PRRS MLV is a live vaccine that contains as active component modified live porcine reproductive and respiratory syndrome (PRRS) virus, strain 96V198, at $10^{2.2}$ -$10^{5.2}$ $CCID_{50}$ per dose. It is indicated for active immunisation of clinically healthy pigs from 1 day of age in a PRRS virus contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRS virus (genotype 1).

Suvaxyn PRRS MLV is presented as lyophilisate and solvent for suspension for injection for intramuscular use. It is intended to be administered as a single 2 ml intramuscular injection to fattening pigs from 1 day of age. Specifically, for breeding gilts and sows, a single intramuscular dose of 2 ml is given prior to introduction into the sow herd, approximately 4 weeks prior to breeding. A single booster dose is given every 6 months.

Following reports of the isolation of a PRRS virus which was believed to be a recombinant of the strains used in two vaccines, Unistrain PRRS and Suvaxyn PRRS MLV, the use of the centrally authorised veterinary medicinal product Suvaxyn PRRS MLV was suspended in Denmark. The recombinant virus appeared to have been transmitted to a boar station and subsequently to swine herds via semen. Establishment of the recombinant virus infection in PRRS-naïve herds via semen was related to clinical signs comparable to manifestations following introduction of virulent PRRSV strains, including fulminant disease. The disease has been confirmed on approximately 40 farms.

The Danish Veterinary and Food Administration suspended the use of the product in Denmark on 5 November 2019 based on the precautionary principle, to protect animal health and prevent new virus variants from occurring in the future. In accordance with Article 45(4) of Regulation (EC) No. 726/2004, on 6 November 2019 Denmark notified the European Commission and the European Medicines Agency of the suspension of the use of Suvaxyn PRRS MLV.

Therefore, on 7 November 2019, the European Commission initiated a procedure under Article 45 of Regulation (EC) No. 726/2004 and requested the CVMP to assess the above concerns and their impact on the benefit-risk balance for Suvaxyn PRRS MLV. The CVMP opinion was requested by 31 May 2020.

## 2. Discussion of data available

Information and clarification concerning the chronology and dates when the MAH first became aware of the potential involvement of Suvaxyn PRRS MLV in relation to the adverse events on the affected farms in Denmark has been provided. The pharmacovigilance actions taken by the MAH in line with Article 49 of Regulation (EC) No. 726/2004 have been described and it can be concluded that the MAH has fulfilled its pharmacovigilance obligations.

In July 2019, PRRSV-1 was detected in samples collected as part of the routine PRRSV surveillance in a PRRSV-negative boar station in Denmark. Semen sales were stopped after the presence of PRRS virus was confirmed. The strain, named "Horsens virus strain" was supposedly detected in around 40 herds that had received semen from the boar station. The clinical signs observed in the herds included reproductive failures, piglet mortality up to 60% and in some cases sow mortality.

The virus collected from the boar station, from a neighbouring herd and from these 40 herds that had outbreaks after receiving semen from the boar station was sequenced and analysed. Full genome sequencing of the Horsens virus strain was performed and has been published in the public database

GenBank in March 2020 (accession number MN603982)[1]. The analysis of the sequence was also published in March 2020 by Kvisgaard *et al*.[2].

The analysis of the genetic sequence of the Horsens virus strain carried out by Kvisgaard *et al.* and an independent analysis performed by the MAH indicated that this strain is a recombinant whose genome is mostly composed of genetic material (RNA) derived from two vaccine strains, Amervac (Unistrain PRRS) and 96V198 (Suvaxyn PRRS MLV), suggesting that the Horsens virus strain emerged as a result of the recombination of these vaccines strains. However, the existence of a short sequence stretch in the open reading frame 3 (ORF3) which is different from both parental strains does not allow to completely rule out the possibility that a third PRRSV strain was also involved in the recombination event. Although Kvisgaard *et al.* considered this possibility unlikely, the relatively large number of mutations observed in this short sequence and the MAH's finding that the sequence is more similar to field isolates than to either of the vaccine strains, would corroborate the MAH's view that it would most likely derive from a third field strain. Following this rationale, the Horsens virus strain could also have emerged as a result of a series of recombination events whereby the Suvaxyn PRRS MLV strain could have recombined with an Amervac-like strain which would have already been circulating in the herd where the recombination occurred.

The MAH addressed the possible risk of recombination of PRRS viruses in general with respect to both field strains and modified live PRRSV vaccine strains, including reversion to virulence, based on the recent findings. Genetic recombination of PRRS viruses cannot be excluded and may therefore occur under field conditions. It is generally acknowledged that such recombination can occur between PRRSV field strains including PRRS MLV strains. This has been known for decades and is well described in scientific literature.

Furthermore, the MAH discussed to which extent the use of Suvaxyn PRRS vaccine virus, which is adapted to recombinant baby hamster kidney cells (BHK-21) cells which express a variant of CD163 PRRSV receptor could contribute to a higher degree of genetic variability that could lead to the emergence of virulent virus variants in susceptible pig populations such as those present in Denmark. While the genetic diversity of PRRSV-1 in a defined region such as Denmark cannot be fully known, the MAH compared the Suvaxyn PRRS vaccine virus with known Danish PRRSV-1 isolates as well as vaccine strains of other approved PRRS MLV. The results of the analysis led to the assumption that the vaccine viruses are more closely related to some Danish field strains than some Danish field strains are related to each other. Based on this, it is considered that the Suvaxyn PRRS MLV vaccine virus does not introduce a level of genetic diversity into pig populations beyond the level of diversity that already exists in the field.

In the present case and based on the available information, no definitive conclusion can be drawn about the level of virulence of the recombinant Horsens virus strain, neither from pharmacovigilance data/the epidemiology of the events, nor from its genomic sequence and not from an experimental study on reproductive parameters conducted by the MAH. Nevertheless, the data provided by the Danish Food and Agriculture Council on production losses in infected herds indicates that clinical signs such as reproductive failures, high piglet mortality and in some cases sow mortality are caused by the Horsens virus strain.

However, recombination events of a PRRS MLV virus with a virulent PRRS field virus or between two PRRS MLV viruses can only occur in the presence of both viruses at the same farm. As a modified live vaccine virus is generally able to replicate in vaccinated pigs, it has also the potential to recombine

[1] Porcine reproductive and respiratory syndrome virus isolate DK-2019-10166-107, complete genome – link (accessed May 2020)
[2] Kvisgaard *et al*. (2020). A recombination between two Type 1 Porcine Reproductive and Respiratory Syndrome Virus (PRRSV-1) vaccine strains has caused severe outbreaks in Danish pigs. doi/10.1111/tbed.13555

with field strains or other vaccine strains that may be concurrently replicating in the same pig. Nevertheless, if such a recombination event would happen, no prediction regarding the virulence and possible effects of the resulting recombinant PRRS virus can be made. Based on the available data, there is no product specific concern identified for Suvaxyn PRRS MLV that is different from other authorised modified live PRRSV vaccines in this respect.

While Suvaxyn PRRS MLV has been identified as one of the components of the recombinant virus, based on the available data there is no evidence to suggest that an increased probability of recombination is linked to this product compared to other modified live PRRS vaccines. In addition, while it is acknowledged that recombination between PRRS viruses can occur and possibly result in clinical signs related to PRRS infection, such events are considered to occur infrequently.

Thus, the well-known general possibility of recombination of PRRSV field strains and PRRS MLV strains and the potential implications of such recombination events should be considered when using modified live PRRS vaccines. In addition, the opportunity for PRRS viruses to circulate and disseminate should be limited by specific precautionary measures (e.g. vaccination, use of vaccines under specific rules, biosafety/biosecurity measures). However, these precautions are relevant not only for Suvaxyn PRRS MLV but also for all modified live PRRS vaccines authorised in the EU.

In order to limit the opportunity for the PRRS MLV viruses to circulate and to reduce this risk and the frequency of recombination between PRRS viruses including PRRS vaccine strains the MAH has proposed risk mitigation measures consisting of warning sentences to be included in the product information, as well as a more general guidance on transitioning from one PRRS MLV vaccine to another within the same farm. This guidance is based on the principle not to use different PRRS MLV vaccines in the same farm at the same time.

The CVMP considered that the proposed warning sentences are in general comprehensible and agreed minor modifications to them. Section 4.5 of the Summary of product characteristics and the corresponding section 12 of the package leaflet should be modified as follows:

*Special precautions for use in animals*

*…*

*Newly introduced PRRS virus-naïve ~~animals~~ females (e.g. replacement gilts from PRRS virus-negative herds) should be vaccinated prior to introduction into the herd of non-PRRS virus-naïve animals and prior to pregnancy.*

*It is advised to vaccinate all target pigs within a herd from the earliest recommended age onwards.*

*In order to limit the potential risk of recombination between PRRS vaccine strains do not use different PRRS MLV vaccines on the same farm at the same time. Do not routinely rotate two or more commercial PRRS MLV vaccines in a herd with the intention to improve cross-protection.*

In addition, the Committee recognised that such warning sentences would also be applicable to other PRRS MLV vaccines authorised in the EU and further considerations on this matter should be given at a future date.

The more detailed guidance proposed for transitioning from one PRRS MLV vaccine to another within the same farm is generally comprehensible as well. However, the implementation of such a guidance is considered not directly related to the product information but more to specific management measures within the farms. Hence, it was concluded that a separate document on the correct and proper use of PRRS MLV vaccines (including transitioning) should be developed.

# 3. Benefit-risk evaluation

**Introduction**

Suvaxyn PRRS MLV is a modified live vaccine containing porcine reproductive and respiratory syndrome (PRRS) virus, strain 96V198, as active component. It is presented as lyophilisate and solvent for suspension for injection.

This vaccine is intended for active immunisation of clinically healthy pigs from 1 day of age in a PRRS virus contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRS virus (genotype 1). The onset of immunity is 21 days after vaccination. The duration of immunity is 26 weeks after vaccination.

**Benefit assessment**

The efficacy of the vaccine has not been reviewed in terms of direct therapeutic or additional benefits in this Article 45 procedure.

**Risk assessment**

The quality and the target animal safety of the product, as well as the risks for the user, the environment and the consumer have not been reviewed in this Article 45 procedure.

Specific potential risks, according to product type and application:

Unintended spread of vaccine strain can occur as the product contains live attenuated virus and live organisms can be introduced into the environment.

Reversion to virulence is possible as the product contains live attenuated virus, which has replicative or integrative potential. However, no indication was observed that after serial passages the vaccine virus reverted to virulence.

As this vaccine strain is also able to replicate in vaccinated pigs, it has the potential to recombine with field strains or other vaccine strains that may be concurrently replicating in the same pig. Genetic recombination of PRRS viruses including PRRS MLV strains is a natural process and cannot be excluded. This feature is generally acknowledged and known for decades and is well described in scientific literature. Considering this background, possible risks related to genetic recombination have been addressed and assessed in the initial marketing authorisation procedure of Suvaxyn PRRS MLV as well as in follow-up procedures.

With regard to the event in Denmark which triggered this Article 45 procedure, it is assumed that the recombinant strain emerged in a pig farm probably by a recombination event that involved two PRRS MLV strains related to the vaccines Unistrain PRRS and Suvaxyn PRRS MLV. While Suvaxyn PRRS MLV has been identified as one of the components of the recombinant virus, based on the available data there is no evidence to suggest that an increased probability of recombination is linked to this product compared to other modified live PRRS vaccines. In addition, it cannot be stated that the sole presence of genomic sequences belonging to Suvaxyn PRRS MLV in the recombinant strain are responsible for the observed virulence. The event in Denmark is considered linked to the introduction of the recombinant virus in PRRSV-naïve herds by transmission via contaminated semen, however this is not considered to be related specifically to the product Suvaxyn PRRS MLV. Therefore, it is considered that this event does not affect the benefit-risk assessment for Suvaxyn PRRS MLV.

**Risk management or mitigation measures**

Appropriate information is already included in the SPC 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. However, the addition of further information in order to decrease the risk of recombination occurring is deemed necessary in the context of this Article 45 procedure (see above).

**Evaluation and conclusions on the benefit-risk balance**

Overall, the benefit-risk balance of Suvaxyn PRRS MLV is considered positive, subject to the provision of additional warnings in the product information.

# Grounds for amendment of the summary of product characteristics and package leaflet

Whereas

- potential for genetic recombination is considered an intrinsic property of PRRS viruses and is well described in scientific literature;
- based on the available data there is no evidence to suggest that an increased probability of recombination is linked to Suvaxyn PRRS MLV compared to other modified live PRRSV vaccines;
- it cannot be stated that the sole presence of genomic sequences belonging to Suvaxyn PRRS MLV in the recombinant strain are responsible for the observed virulence;
- the addition of further warnings to the product information in order to decrease the risk of recombination occurring has been recommended;
- the CVMP concluded that the overall benefit-risk balance of Suvaxyn PRRS MLV remains positive;

the CVMP has recommended the amendment of the marketing authorisation for Suvaxyn PRRS MLV as referred in Annex A.