FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
8 rue Claude Bourgelat
Parc d'activités de la Grande Marche - Javené
BP 90203
35302 Fougères Cedex
France

"MUTUAL RECOGNITION " PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0253/001/MR
Name, strength and pharmaceutical form	POULVAC IB QX Lyophilisate for suspension for spray application
Applicant	Pfizer Holding
Active substance(s)	Live Infectious Bronchitis Virus, strain L1148
ATC Vetcode	QI01AD07
Target species	Chickens
Indication for use	Active immunisation against Infectious Bronchitis in order to reduce respiratory signs due to the virus IB QX like strain

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual recognition application in accordance with Article 31 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	20/03/2013
Date product first authorised in the Reference Member State (MRP only)	04/01/2011
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, HU, IE, IT, LV, IT, NL, PL, PT, RO, SI, SK, UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the renal lesions observed after an overdose application are indicated in the SPC. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

Composition :

Active substance :

Live attenuated Avian Infectious Bronchitis virus, strain L1148	$10^{3.0} – 10^{5.0}$ EID_{50}/dose

Excipients per mL :

D-mannitol	50.0 mg
Gelatine	70.7 mg
Inositol	50.0 mg
Peptone	65.0 mg
Water for injection	QSP 1 mL

The container system is 3 mL hydrolytic type I glass vials closed with chlorobutyl stoppers and aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulation of monographs 3.2.1 and

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3.29 of the European Pharmacopoeia.

The choice of the vaccine strain, of the vaccine composition, of the dose volume and vaccination schedule are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. Relevant manufacturing licences and GMP certificates are enclosed.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

Starting materials of non-biological origin used in production comply with indicated pharmacopoeia monographs.

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur (monographs 5.2.2 and 2.6.24) ; any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control tests during production

The tests performed during production are described in detail. They are germ count and titre determination. These tests have been adequately validated.

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. Relevant validations are provided.
The tests include in particular :
- visual inspection and vacuum testing
- virus identity
- virus titration
- germ count test

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- *Mycoplasma* according to Ph Eur 2.6.7
- absence of extraneous agents according to Ph Eur 2.6.25
- residual humidity

The demonstration of the batch to batch consistency is based on the results of 3 batches per site produced according to the method described in the dossier. Results of 3 batches of active ingredient are also provided.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance (15 months) when stored under the approved conditions (-50°C)

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (18 months) when stored under the approved conditions (2-8°C). According to the stability data, an overage in titre is performed to ensure the minimal guaranteed dose at the end of the shelf-life.

The in-use shelf-life (2 hours) of the reconstituted vaccine is supported by the data.

III. SAFETY ASSESSMENT

The vaccine is supplied in a multi-dose, lyophilized cake which is reconstituted by the end user for mass application through coarse spray. Vaccination is recommended on broilers chickens from day of age and for breeders and layers from 1 week of age.
Safety studies have been performed with vaccine batches produced according the described production process.

Laboratory trials

The trials have been performed on SPF chickens.

The safety of the administration of an overdose and the repeated administration of one maximum dose in the target animal is demonstrated in 4 laboratory trials.

Groups of 17 or 20 vaccinated day old animals are used in each study, control unvaccinated groups are included in parallel. Administration route is the one recommended by the Ph Eur monograph 0442 (eye drop). A study is performed using the recommended route.
Animals are followed for clinical signs and ciliostatis score according to the Ph Eur monograph 0442.
The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.
The vaccine is demonstrated safe. Renal lesions are induced after the administration of overdose and are indicated in the SPC.

Effects on reproductive performance were examined in four laboratory studies. Groups of 50 vaccinated day old or 7 day old animals are used in each study, control unvaccinated groups are included in parallel Administration route is the

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one recommended by the Ph Eur monograph 0442 (eye drop). Animals are followed for cytoplastics oviducts according to the Ph Eur monograph 0442.
The safety in laying hens was studied. Two groups of one-day old SPC chickens without IBV antibodies were used. One group of 42 animals is left unvaccinated whereas a group of 41 birds is vaccinated. The vaccine scheme includes a first vaccination with a maximum dose at day 7 of age and a second vaccination with a 10-times maximum dose (10^6 EID_{50}/bird) at day 150 of age.
The follow-up consists of monitoring of body weights, clinical signs, ciliostasis, gross pathological examination of the oviduct, egg production and quality of the egg.
Results are showing no difference between vaccinated and controls animals for the monitored parameters. The pattern of body weight gains and laying performances are similar and in accordance with the awaited ones for such animals. Egg abnormalities are not increased in the vaccinated group.
The conclusion of this study is that the vaccination at an early stage of the laying period with Poulvac IB QX does not affect the laying performances.

Two additional studies were performed in commercial one-day-old future layers or breeders with maternally derived antibodies.
In the first study, after vaccination of 40 chickens with the maximum dose of vaccine, no macroscopic oviduct lesions were found at necropsy in any animal vaccinated.
In the second study, after vaccination of 50 chickens with the maximum dose of vaccine, three birds showed abnormalities in the left oviduct. Nevertheless, as the cyst was located in the wall of the oviduct it may be considered that it will have no impact on the ovarian conduct itself.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.
The vaccine is demonstrated safe for reproductive tracts when administered in 7 day old animals. The SPC mentions that future layers and breeders should be vaccinated from 7 day of age. The vaccine may be administered as early as 1 day of age to future layers or breeders with MDAs against IBV.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study was not carried out.

Specific studies were carried out to describe the spread, dissemination, and reversion to virulence of the live vaccine strain.
One laboratory study investigates spread and dissemination. The vaccine strain is able to spread from vaccinated to unvaccinated animals until 14 days but no clinical sign is associated with the spreading. The vaccine strain is also able to disseminate in the body of vaccinated animals (pancreas, respiratory tract, kidneys and lungs) but no clinical sign is associated.
Two laboratory studies investigate the reversion to virulence according the Ph Eur 0442 requirements, using five passages on chickens. No increase in virulence is observed.

No specific studies are provided for biological properties and recombination or genetic reassortment of the vaccine strain(s). The vaccine strain induces low ciliostasis and minor kidney lesions. Recombination with field strain is considered

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not likely to have a negative impact on the disease situation.

The adjuvant and excipients used are included in table 1 of the MRL regulation. Based on this information, no withdrawal period is proposed.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Field studies

A safety field study performed on 3 farms in France, including 83872 chickens is provided. Animals were vaccinated with Poulvac IB QX or a placebo by nebulisation. All animals were followed for clinical signs and rearing performances. In order to further support the safety of the vaccination in the laying period, the applicant performed a field study in France. A total of 48092 laying hens have been involved in 3 different sites. Before study, all the animals received a standard vaccination program. During the study, only Poulvac IB QX or water have been administered. Indeed 23577 animals have been spray vaccinated with Poulvac IB QX using a commercial dose (10^3-10^5 EID_{50}/bird) whereas 24515 control animals received only water by spray route. The animals were 22 weeks old when they received the tested article. After the vaccination, the animals were followed for clinical signs during 7 weeks. Egg production as well as egg quality were monitored. 1, 2 and 3 weeks after vaccination, tracheal swabs are collected for IBV detection by RT-PCR.
Results are showing that neither clinical signs nor adverse reactions occurred excepted for a reduction in feed intake between 5 and 9 days after vaccination on one site for both groups. Also no difference in laying performances (egg quality and percentage of laying per day) is observed between vaccinated and control animals. And no IBV has been isolated from tracheal swabs. The conclusions of the studies are in line with those from the laboratory study.

Ecotoxicity

The applicant provided an environmental risk assessment which showed that the risk for the environment and other animals and species posed by this vaccine should be considered due to spreading to non-vaccinated animals.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. EFFICACY

The efficacy of the product has been demonstrated in laboratory challenge studies in accordance with the following Ph.Eur. monograph:

Avian Infectious Bronchitis Vaccine (Live) : monograph 0442

The efficacy on the target species chickens was demonstrated in SPF animals at the minimum age recommended for vaccination and administered via coarse spray.
Minimum dose were used in all efficacy studies.

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Efficacy studies have been performed with vaccine batches produced according the described production process.

The challenge strain used in the efficacy studies belongs to the group of variant IBV QX like strains as the vaccine strain. It was administered by eye drop.

IV.B Laboratory Trials

An onset of immunity laboratory trial has been performed in one day old SPF chickens. 22 animals per group have been vaccinated with different doses of vaccine or not vaccinated and challenged 21 days post vaccination. 5 days later ciliary activity in tracheal explants and any lesions of kidneys and trachea have been recorded.
The study fulfils the Ph Eur recommendations when animals are vaccinated with the minimal recommended vaccine dose.

An efficacy study in presence of maternal derived antibodies has been performed. The study included chickens with maternal derived antibodies and SPF chickens (30 per group). Animals have been vaccinated with minimum recommended dose of vaccine or unvaccinated and challenged 21 days later.
Ciliary activity in tracheal explants has been recorded.
No interference of the MDA on the efficacy of the vaccine is shown.

Thirdly, a duration of immunity laboratory trial has been performed. Vaccinated animals with the minimum recommended dose and unvaccinated animals (30 per group) have been challenged 63 days after.
Ciliary activity in tracheal explants has been recorded.
The study fulfils the Ph Eur recommendations.

The following conclusions can be drawn from the results of the efficacy studies : For active immunisation of chickens in order to reduce respiratory signs of Infectious Bronchitis caused by QX-like variants of Infectious Bornchitis virus.

Onset of immunity occurs from 3 weeks after vaccination.
The duration of immunity lasts 63 days after vaccination.

The vaccination scheme is as follows :
In broilers : one dose of vaccine from one day of age by spray vaccination. In future layers or breeders : one dose of vaccine from 7 days of age by spray vaccination. The vaccine may be administered as early as 1 day of age to future layers or breeders with MDAs against IBV.

Field Trials

One efficacy field study performed on 3 farms in France, including 83872 chickens is provided. Animals were vaccinated with Poulvac IB QX or a placebo by nebulisation.

After follow-up on the farms, 25 animals per group are transferred into the laboratory to be challenged. Ciliary activity and kidneys lesions are followed. The study supports the conclusion from the laboratory trials.

V. OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in

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accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the

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quality, safety and efficacy of the veterinary medicinal product.

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This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
Variation FR/V0235/001/II/006: SPC revision informing the user that - the vaccine can be used during the laying period. - the size of the droplet should be greater than 100 µm	III: safety	January 2015
Variation FR/V/0253/001/II/012: SPC revision informing the user that - The vaccine may be administered as early as 1 day of age to future layers or breeders with MDAs against IBV - When vaccination is planned in future layers or breeders younger than 7 days, the parent flock should be vaccinated with an IB vaccine to ensure progeny with MDAs against IBV.	III: safety	June 2019

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