ANSES

Agence Nationale du Médicament Vétérinaire
(National Agency for Veterinary Drugs)
(Reference Member State)
BP 90203
35302 FOUGERES CEDEX
FRANCE

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Aquavac Vibrio Oral

Update 14/11/2016

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0165/001/MR
Name, strength and pharmaceutical form	Aquavac Vibrio Oral
Applicant	Initial: Schering-Plough Vétérinaire 92, rue Baudin 92307 LAVALLOIS-PERRET Cedex France Current : Intervet Rue Olivier de Serres Angers technopole 49070 BEAUCOUZE ; FRANCE
Active substances	• Inactivated cells of *Listonella* (*Vibrio*) *anguillarum* strain 78-SKID,RPS_{60}(*) > 60% • Inactivated cells of *Vibrio ordalii*[1] strain MSC 275, RPS_{60}(*) > 60% *RPS: relative percentage of survival at 60% of mortality of the controls
ATC Vetcode	ATC Vet code QI10BB01
Target species	Rainbow trout (Oncorhynchus mykiss)
Indication for use	For the active immunisation of fish to reduce mortality due to vibriosis caused by *Listonella (Vibrio) anguillarum* and *Vibrio ordalii*[1]. Onset of immunity: 336 degree-days in case of use of Aquavac Vibrio Oral as a primary vaccine. A duration of immunity has not been demonstrated beyond this. For fish vaccinated by immersion with Aquavac Vibrio Immersion and Injection and revaccinated with Aquavac Vibrio Oral, protection was seen after 336 degree days.

[1] *Vibrio ordalii* is a subset of *Listonella* (*Vibrio) anguillarum* O2

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual recognition application in accordance with Article 32 (2) of Directive 2001/82/EC as amended
Date of completion of the original mutual recognition procedure	05/07/2006
Date product first authorised in the Reference Member State (MRP only)	12/01/2005
Concerned Member States for original procedure	CY,DK,EL,ES,FI,IE,IT,MT,PT,SI,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 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

The product contains :

- Inactivated cells of *Listonella* (*Vibrio*) *anguillarum* strain 78-SKID, inducing a relative percentage survival in vaccinates, at time of 60% of mortality in controls, after oral vaccination and subsequent challenge, of at least 60%

- Inactivated cells of *Vibrio ordalii*[2] strain MSC 275, inducing a relative percentage survival in vaccinates, at time of 60% of mortality in controls, after oral vaccination and subsequent challenge, of at least 60%

The product also contains less than 0.5 mg/mL of formaldehyde, residue of the inactivation of the active ingredients.

The containers consist of 1 litre high density polyethylene containers, with bromobutyl stopper and aluminium sealing ring. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains, formulation, and absence of preservative are justified.

The inactivation process is correctly validated.

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 in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

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

C. Control of Starting Materials

The active substances are:
- *Listonella* (*Vibrio*) *anguillarum* strain 78-SKID,
- *Vibrio ordalii*[3] strain MSC 275.

The active substances are manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin used in production comply with European pharmacopoeia monographs where these exist, or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines.

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.

[2] *Vibrio ordalii* is a subset of *Listonella* (*Vibrio) anguillarum* O2
[3] *Vibrio ordalii* is a subset of *Listonella* (*Vibrio) anguillarum* O2

E. Control tests during production

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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. The tests include in particular appearance, volume filled, viscosity, conductivity, batch potency test (by challenge), residual formaldehyde content, safety test in target species, sterility, inactivation control.

Batch potency test: Two groups of 100 rainbow trouts each, weighing 10-25 g, are used. One group receives 0.2 ml of vaccine per fish by oral route, the other serves as control. Both groups are maintained for 28 days at 12-15 °C. The fish are then challenged : 50 vaccinates and 50 controls being inoculated with a virulent strain of *V. anguillarum* (VIB 1), 50 vaccinates and 50 controls being inoculated with a virulent strain of *V. ordalii* (VIB 2). The fishes are maintained until 60 % specific mortality is reached in the controls. At least 60 % of the control group must die within the 21 days following challenge. The RPS for the vaccinated fishes must be not less than 60 %, calculated at the time corresponding to 60 % mortality in the controls (RPS = (1 - % vaccinate mortality / % control mortality) x 100)

The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

The storage of the antigen prior to formulation was considered acceptable because the potency of the vaccine at release is checked through challenge.

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 when stored under the approved conditions.

After mixing with feed pellets, stability was established by vaccination with the vaccine/feed pellets stored up to 21 days and subsequent challenge of fish. The protection afforded by the vaccine treated pellets stored up to 10 days at ambient room temperature was satisfactory. Fungal contamination of the vaccine treated pellets was observed after 21 days of storage, associated with reduction of the efficacy of vaccination after 14 and 21 days of storage, justifying the in use-stability indicated in the SPC.

III. SAFETY ASSESSMENT

The vaccine is formulated to a target concentration for both components. It is inactivated and the control of the active ingredients at the level of the final product is performed by a challenge test in the target species.

The concept of maximum potency was not deemed appropriate for this product. It was considered by the RMS that any batch formulated to these target concentrations and with a compliant batch potency test result was appropriate to support the demonstration of the safety of the vaccine.

Laboratory trials

The safety of the administration of one dose and an overdose in the target species is demonstrated in the following studies:

- in rainbow trout (vaccination at 12°C):
    - pivotal study: in 12g fish at 12°C, 300 fish receiving a normal dose, 300 fish receiving a double dose and 300 controls. Observation of 28 days
    - other study: priming by immersion of 300 fish at a size of 12g with a single dose of Aquavac Vibrio Immesrion and Injection and revaccination 2 months later at the size of 14g with a single dose of Aquavac Vibrio Oral. Observation of 28 days

The safety of the repeated administration of one dose was not investigated, which is acceptable because the vaccine is intended to be used once in the lifetime of the fish.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

No adverse reaction were observed.
The SPC reflects these results; despite several field trials were conducted in sea bass, the indication for sea bass was not adopted because of the absence of safety studies under laboratory conditions and limited demonstration of efficacy in this species (see also next chapter).

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals.

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.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

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

The interaction of the vaccine with Aquavac Vibrio Oral was studied. 12g rainbow trout were vaccinated with a single dose of Aquavac Vibrio Immersion and Injection and a revaccination was conducted in the fish at the size of 14g

with a single dose of Aquavac Vibrio Oral. No adverse reaction were observed. Efficacy of this protocol was also studied (see next chapter). Therefore, the possible association of both products is indicated in the SPC.

Field studies

In rainbow trout:

About 70,000 rainbow trout of 28.5g were vaccinated by immersion at a temperature of 10-13°C; a revaccination with Aquavac Vibrio Oral was performed 11 weeks later, when the fish were of a size of 83.1g. 110,000 controls were included. No abnormality was seen.

In sea bass:
Six different studies involving millions of sea bass from 60 g to 800 g, either primed or not, vaccinated or revaccinated with Aquavac vibrio oral after a priming. No adverse effects were reported.
For the record, as far as no safety test under laboratory conditions was performed and the follow-up under field conditions was very limited, the indication in sea bass was not accepted.

Ecotoxicity

The applicant provided an argumentation which showed that no further assessment is required.

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

IV CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show:

- in rainbow trout (vaccination at 12°C):
    - efficacy of priming
        - pivotal study: in 12g fish, vaccination of 300 fish and challenge 28 days later of 150 fish with Vibrio anguillarum (VIB1) and 150 fish with Vibrio ordalii (VIB2); same number of fish included as controls. The relative percentage of protection (RPS) was between 75 and 90%.
        - other studies: hundreds fish of 6 to 12g, receiving a single dose of vaccine were challenged 28 days after vaccination with the same strains. The relative percentage of protection (RPS) was between 73 and 100%.
    - Efficacy as revaccination after priming with Aquavac vibrio Immersion and Inection

- pivotal study: 600 fish were primed at 12g with Aquavac vibrio Immersion and Injection and revaccinated; of these, 300 were revaccinated with Aquavac Vibrio Oral 2 months later at 14g and 300 were not revaccinated; 300 other fish were included as controls. All fish were challenged either against VIB1 or VIB2 28 days later. RPS was between 98 and 100% in revaccinated fish and between 82 and 100% in fish receiving no revaccination.

Field Trials

The applicant has conducted field studies in about 180,000 rainbow trout (including 70,000 vaccinates) and 176,000 sea bass (including 53,000 vaccinates). As the field challenge could not be objectivated and other vaccines were also administered, the improved results observed in vaccinates cannot be attributed with certainty to Aquavac Vibrio Oral.
Several studies were also conducted in Sea Bass of 4g and over, primed or not with Aquavac Vibrio Immersion and Injection. However, due to the field conditions (difficulties to objectivate a challenge, use of other commercial vaccines in controls…), it was not possible to ascertain the efficacy; therefore, there is no indication for sea bass.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in 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 quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website.

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.

Quality changes

Summary of change	**Approval date**
Change in primary packaging (addition of supplier of HDPE)	**2012**