Food and Agriculture Organization of the United Nations

European Commission for the Control of Foot-and-Mouth disease

EuFMD FMD VACCINE PREQUALIFICATION PUBLIC SUMMARY REPORT

Adopted by the Standing Committee for Prequalification of vaccines against FAST diseases (SCPQv)

Name of Foot-and-Mouth Disease Vaccine
AFTOPOR

Manufacturer/Applicant
Boehringer Ingelheim Animal Health

Prequalification number
PQv22-006

Date adopted by the SCPQv
21 Nov 2023

Date added to the list of prequalified FMD vaccines (PQv list):
07 Dec 2023

The Public Summary Report (PSR) is a modified version of the full Evaluation Report (ER) considered by the SCPQv with all information of a commercially confidential nature removed.

Contents

Background and basis for prequalification listing

This public summary report for **AFTOPOR**, manufactured by **Boehringer Ingelheim Animal Health** has been produced following evaluation of an application for prequalification in line with the 'Administrative Procedure for Applications for Prequalification (PQv) of Foot-and-Mouth Disease Vaccines'. The technical requirements applied are those described in 'Technical Guidance for Application for Prequalification of Foot-and-Mouth Disease Vaccines and Content of the Prequalification Evidence File' with the aim of assuring compliance with at least minimum international standards i.e., the standards defined in the general and specific chapters of the latest version of the Manual of Diagnostic Tests and Vaccines for Terrestrial Animals of the World Organization for Animal Health (the' WOAH Terrestrial Manual').

The Public Summary Report (PSR) is a modified version of the full Evaluation Report (ER) considered by the Standing Committee on Prequalification of Vaccines against FAST diseases (SCPQv) with all information of a commercially confidential nature removed. Further information on the role of the SCPQv in the governance and decision process for the prequalification of FMD vaccines can be found at: https://www.fao.org/eufmd/who-we-are/structure/scpqv.

PQv uses a risk-based approach to focus the data requirements on critical elements of FMD vaccine manufacture and testing supported by evidence that the vaccine holds a full marketing authorization (MA)/product registration issued by a National Regulatory Authority (NRA). PQv does not attempt to repeat the evaluation performed by the national regulatory authority(ies) specified in Annex 1 for the purposes of marketing authorization but uses the outcome from the national evaluation procedure(s) as part of the evidence for qualification assurance together with additional information on key properties of the vaccine and its manufacture.

PQv provides an independent and internationally recognized source of information on FAST vaccines that can be used by EuFMD member nations and other parties seeking to control FAST diseases through vaccination. Further details of the PQv scheme can be found at https://www.fao.org/eufmd/global-situation/vaccine-prequalification/key-principles/ or by contacting EuFMD at EuFMD-PQv@fao.org.

Introduction

On **27 April 2023**, the applicant **Boehringer Ingelheim Animal Health** submitted an application for prequalification for AFTOPOR.

The Prequalification Evidence File (PEF) was submitted in line with the requirements of the 'Technical Guidance for Application for Prequalification of Foot-and-Mouth Disease Vaccines and Content of the Prequalification Evidence File'.

The Standing Committee for Prequalification of FAST vaccines (SCPQv) adopted the vaccine for PQv Listing at its meeting on **21 Nov 2023**.

The vaccine is indicated for **cattle, sheep and pigs** against **FMD serotypes O, A, Asia1, SAT (multistrain vaccine with between 1 and 8 strains per dose).**

The route of administration is **intramuscular (all target species).**

The vaccine is a **water-in-oil-in-water emulsion vaccine adjuvanted with mineral oil.**

The primary vaccination schedule is **two doses four weeks apart**.

A booster dose is recommended every **four months in pigs, and every six months in cattle and sheep.**

The vaccine is manufactured by **Boehringer Ingelheim Animal Health in conformity** to the principles of EU Good Manufacturing Practice (GMP) as certified by the national regulatory authority for GMP **VMD [Veterinary Medicines Directorate, UK; for Boehringer Ingelheim Animal Health, Pirbright, UK] and ANMV/ANSES [for Boehringer Ingelheim Animal Health, Laboratoire Portes des Alpes, France].**

The manufacturing site meets the relevant standards of biosafety and biosecurity preventing release of pathogens from sites of manufacture into the environment as certified by the national regulatory authority for biosafety/biosecurity: **SAPO licence issued by the Health and Safety Executive, UK**

Address of manufacturing site(s):
Antigen production, formulation, filling, ~~and~~ packaging and QC testing take place at:
Boehringer Ingelheim Animal Health
Ash Road
Pirbright
Surrey, GU24 0NQ
United Kingdom

Storage of the active substance, formulation, filling, packaging and QC testing may also take place at:
Boehringer Ingelheim Animal Health
Laboratoire Porte des Alpes
698 00 Rue De L'Aviation
Saint Priest, France

Secondary packaging may also take place at:
Chemin de Cruzols 69210
Lentily, France

In vitro testing, chloroform test, may be performed at two sites:
Reading Scientific Services Limited, Reading, UK
Cebiphar, France

In vivo testing may be performed at:
BIAH 01150
St Vulbas France

Annex 1. Summary of evidence provided to support PQv Listing for AFTOPOR

Definitions

Qualification Assurance	Prequalification of vaccines by EuFMD is based on the principle of 'Qualification Assurance'. Qualification of vaccines is performed by national competent authorities through granting a national marketing authorization (also termed product license or registration in some areas) based on a comprehensive evaluation of evidence demonstrating the pharmaceutical quality, safety and efficacy of the product in line with respective national legislation. Only vaccines for which a national marketing authorization has been issued by at least one national competent authority are eligible for PQv. PQv does not attempt to repeat the evaluation carried out by NRA but relies on a risk-based evaluation of evidence provided by the applicant in the prequalification evidence file (PEF) to demonstrate that the vaccine meets at least the minimum standards in the WOAH Terrestrial Manual with respect to the key properties of the vaccine that are essential for its safe and effective use. The outcome of prequalification is an assessment of the level of assurance that can be placed on the qualification that exists for the vaccine. The level of assurance is rated from 'Assurance', through 'Partial Assurance' to 'Insufficient evidence' to recognize that the level of assurance depends on the amount and quality of data provided. In the case of vaccines rated 'Partial Assurance' or 'Insufficient Evidence', the outcome of PQv does not call into question the evaluation performed by a national competent authority in qualifying the vaccine but only reflects that data has not been provided to EuFMD to demonstrate compliance with the minimum standards of the WOAH Manual. The PQv Technical Guidelines clarifies the interpretation of the standards defined in the WOAH Manual that will be applied by the Standing Committee on Prequalification of Vaccines in order to provide certainty to applicants in situations where the Manual is open to interpretation.
Assurance	Prequalification evidence provided assurance that the product meets at least the minimum international standards of the WOAH Terrestrial Manual as further elaborated in the PQv Technical Guidelines.
Partial Assurance	Some prequalification evidence was provided to assure that the product meets at least the minimum international standards of the WOAH Terrestrial manual, but the evidence was not sufficient to provide full assurance as elaborated in the PQv

	Technical Guidelines. An explanation of the basis for the assignment of this category will be included in the summary of evidence.
Insufficient evidence	Insufficient prequalification evidence was provided to assure that the product meets at least the minimum international standards of WOAH Terrestrial manual as further elaborated in the PQv Technical Guidelines. An explanation of the basis for the assignment of this category will be included in the summary of evidence.
N/A	Not applicable.
Additional information	Additional information is provided in this report where evidence is provided to demonstrate that the standards of manufacture and/or testing meet another internationally recognized standard, for example PIC/S or VICH, or that the evidence provided goes beyond the minimum international standards of WOAH Terrestrial manual.

Country/region where Marketing Authorisation/ Product Registration	Marketing Authorisation/Product Registration Reference number & Date issued	PQv standard
AUSTRALIA		*Assured*
FRANCE	*FR/V/6308186 0/2017*	
GERMANY		
HONG-KONG		
INDONESIA		
IRAN		
ISRAEL		
LEBANON		
MALAYSIA		
NEW ZEALAND		
SOUTH KOREA		
TAIWAN		
THAILAND		
UNITED KINGDOM		
UNITED STATES OF AMERICA		
VIETNAM		

PEF Heading/ Section		Prequalification evidence to support PQv listing	PQv standard
1.A	Site Master File (SMF) and evidence of GMP	Valid GMP certificates issued within last three years were provided, for the manufacturing sites involved in the manufacturing process, to the standards of WHO. The GMP certificates are valid until February 2025.	*Assured*
	NRA for GMP	VMD (Veterinary Medicines Directorate, UK) ANMV/ANSES	
1.A.1	Biosafety & Biosecurity	Specified Animal Pathogens Order (SAPO) licence valid until 1 July, 2025.	*Assured*
	Health and Safety Executive	Health and Safety Executive, UK	
1.B	Summary Product Characteristics (SPC)	A SPC following the format of the EU QRD text (v8.2) was provided.	*Assured*
1.C	Labelling and package insert	Labels for 20, 50, 100, 200 and 300 ml and package insert were provided. Information on product label includes the following sections: target species, dose, route of administration, withdrawal period, batch no., expiry date, and on the 100 – 300 ml bottles also pharmaceutical form, efficacy claims, storage, and MAH. Label claims are supported by safety and efficacy studies that comply with the WOAH standards for FMD.	*Assured*
1.D.	Lot summary protocol	A one-page summary certificate of analysis was provided for 7 batches formulated at the two different sites between 2013 and 2016.	*Assured*

Chapter 2	Manufacture & Control		
2.A	Composition	A table of the qualitative and quantitative composition of the vaccine with details of the antigen content, adjuvants, excipients, and preservative, expressed per dose is provided. One dose of 2 mL of AFTOPOR contains between one and eight antigens (>6 PD_{50}/strain) in a water-in-oil-in-water emulsion adjuvant.	*Assured*
2.B	Method of Manufacture		
2.B.1	Description of manufacturing process	A flow chart of the manufacturing process has been provided to outline the different production steps from working seed virus to finished product. Within the flow chart the in-process tests are listed. The method of manufacture including the inactivation procedure using a two-vessel system is compliant with the requirements for FMDV vaccines described in chapter 3.1.8 WOAH Terrestrial Manual 2021. Binary ethyleneimine (BEI) is used as the inactivant in a two-step process. The inactivation kinetics is carried out on each batch of viral culture and a check of residual live virus performed. Summary information provided from 7 historical batches (non-consecutive) from the two manufacturing sites outlining the characteristics of the batches, in-process and finished product	*Assured*

		tests and test specifications. All tests were within the defined specifications. Batches included between 3 and 8 strains. Although these are not consecutive the batches support consistency of production.	
2.B.1.a	Validation of the inactivation process	The validation report for the inactivation kinetics has been provided. Satisfactory information is provided to confirm compliance with WOAH requirements.	*Assured*
2.B.2	Detailed flowcharts	A detailed flowchart of the production steps for AFTOPOR was provided from the working seed to filling and labelling of the finished product. The flowchart included the In Process and Final Product quality control tests.	
2.C	Production and Control of Starting Materials		
2.C.1	Starting materials of biological origin		
2.C.1.1	Virus Seed	Information relating to each of the seed materials is provided and includes detailed information on origin, history, MSV designation, control tests on the MSV (bacterial and fungal, mycoplasma, identity, viral purity, extraneous agents, titration, working seed virus and storage). The applicant reported tests were performed to Ph. Eur plus in addition some 9CFR. The WSV is at most 3 passages from the MSV. Tests on the working seed virus include infective titre. Both the MSV and WSV are stored at ≤-70°C.	*Assured*

		A BSE/TSE risk assessment is included which addresses the potential areas of risk.	
2.C.1.2	Cell seed	The applicant reported that the MCB and WCB are fully tested in compliance with Ph. Eur.	*Additional information*
2.D	In-Process Controls		
2.D	In-process controls	Information has been provided on the infectivity assay and inactivation kinetics, which are performed on each batch of vaccine following the 1st inactivation step. The inactivation process is compliant with WOAH standards. The inactivation test to confirm complete inactivation has been described and the method and validation of the method has been provided. The FMD antigen mass (146S) content has been briefly described and limits set. The 146S antigen content of each batch of bulk inactivated antigen is determined by sucrose density gradient centrifugation. The method and validation report have been provided. No test for residual inactivant is performed. The suitability of the manufacturing method to Eliminate BEI through downstream production processes (purification step) has been demonstrated over decades of commercial batch production.	*Assured*
2.E	Controls on Finished Product		
2.E.1	General characteristics of the finished product	A list of all tests performed, and the release specifications were provided.	*Assured*
2.E.2	Identification of active substance(s)	A description of the final product identity/potency test performed on each batch or corresponding trial blend was	*Assured*

		provided. A validation report has been provided using a vaccine strain which was confirmed to be representative of the vaccine strains included in the vaccine.	
2.E.3	Batch potency	A description of the final product identity/potency test performed on each batch or corresponding trial blend was provided. Information has been provided on the use of this test as a potency test and the pass level set. A batch is released with a VNT titre in serum from vaccinated cattle determined to relate to ≥6 PD_{50} per strain per dose.	*Assured*
2.E.4	Identification and assay of adjuvants	The adjuvant is characterized in the finished product by tests on appearance, emulsion type and viscosity	*Additional information*
2.E.5	Identification and assay of excipients components	A preservative is included in the vaccine. A brief description has been provided on the finished product test which is performed on each batch of vaccine to check the preservative content is within the specifications set.	*Additional information*
2.E.6	Safety tests	Target animals batch safety tests are not performed.	*Additional information*
2.E.7	Sterility test	The applicant reported a sterility test is performed on each batch in accordance with chapter 2.6.1. of the Ph. Eur. “sterility”	*Additional information*
2.E.8	Purity test	A purity test is not performed on the final product. The DIVA properties of the vaccine have been studied and report the ability of the AFTOPOR manufacturing process to remove FMD non-structural proteins in the final product are supported. The manufacturing process is standardized for all FMD antigens	*Assured.*

		therefore the test for NSP on each finished product batch is not required or performed. This is in compliance with WOAH.	
2.E.9	Inactivation test	Inactivation at production scale is performed using a two-vessel system and complies with international and WOAH requirements. The inactivation kinetics is carried out on each batch of viral culture and a check of residual live virus performed.	*Assured.*
2.F	Batch consistency		
2.F	Batch consistency – Process validation	Summary information provided from 7 historical batches (non-consecutive) from the two manufacturing sites outlining the characteristics of the batches, in-process and finished product tests and test specifications. All tests were within the defined specifications. Batches included between 3 and 8 strains. Although these are not consecutive the batches support consistency of production.	*Assured*
2.G	Stability		
2.G	Stability	Stability of 4 batches tested regularly for potency by a serological potency test have been provided and shown to be stable for 18 months. Additionally, stability of 6 batches tested regularly for physico-chemical and serology (potency) have been provided and shown to be stable for at least 18 months.	*Assured*

Safety & Efficacy data requirements for the PEF

PEF Heading/ Section		Prequalification evidence to support PQv listing	PQv standards
Chapter 3	Safety & efficacy section – Use in target species		
3.B	Safety Requirements		
3.B.1	Laboratory studies	A summary of the laboratory safety studies in cattle, sheep and pigs is provided. Safety studies were conducted with a single, double and repeat dose. Some of the safety studies were designed to include groups with vaccines formulated to contain the maximum antigen content and representative serotypes. The safety warnings on the SPC/label/package leaflet reflect local and systemic reactions observed in the safety studies. A warning has been included on the SPC/label/package leaflet that safety in pregnant and lactating animals has not been studied under controlled laboratory conditions but experience in the field showed that vaccination of these animals is safe. No specific studies have been conducted to investigate interactions with other veterinary medicinal products and an appropriate warning has been included in the SPC/label/ package leaflet.	*Assured*
3.B.2	Field studies	Although evidence from field safety studies is not required in the PEF at the initial application stage field studies have been performed in cattle and pigs in outbreak situations using commercial batches of vaccine with satisfactory results.	*Additional information*
3.B.4	User safety	Considered limited risk. The potential user exposure is considered limited as the vaccine may only be administered by competent end users, i.e. a skilled veterinarian or a trained person under supervision of a veterinarian.	*Additional information*

3.B.5	Consumer safety	Evidence not required in the PEF at the initial application stage. A zero day withdrawal period has been established based on all pharmacologically active substances either not requiring an MRL or being considered outside of scope with regard to MRL requirements (or GRAS – generally recognized as safe)	*Additional information*
3.C	Efficacy requirements (including DIVA claims)		
3.C.1	Laboratory studies.	The efficacy of each vaccine strain was demonstrated for cattle using the potency challenge test. One PD_{50} (50 percent cattle protective doses) challenge test was performed using each vaccine strain to establish efficacy in cattle and demonstrating the vaccine contained >6 PD_{50}/dose. Onset of immunity (OOI) was demonstrated by challenge, where cattle and pigs were vaccinated with a single dose of monovalent vaccine (one representative strain) and challenged 7 days later or alternatively by indirect (in-contact with laboratory infected animals) challenge 4 days post vaccination in sheep. Additionally, a serology study was conducted in cattle over 18 months of age (with a quadrivalent vaccine, 2 doses at 0 and 56 days) and a serological response with mean neutralizing antibody levels over the level relating to 6 PD_{50} (as required by WOAH for inactivated vaccines) was observed within 10 days of vaccination. Duration of immunity (DOI) was demonstrated by challenge, where cattle were vaccinated with a single dose of monovalent vaccine (one representative strain) and challenged 6 months later. Additionally, serology studies were conducted in cattle and pigs. In cattle, a quadrivalent vaccine was administered as recommended (2 doses 4 weeks apart) and further booster vaccinations were	*Assured*

		administered. A serological response with mean neutralizing antibody levels over the level relating to 6 PD_{50} (as required by WOAH for inactivated vaccines) was observed, which continued to 6 months and increased following booster vaccinations. In pigs a single dose of a monovalent vaccine (one representative strain) was administered and 2, 3, or 4 months later a second dose was administered. A serological response with mean neutralizing antibody levels over the level relating to 6 PD_{50} (as required by WOAH for inactivated vaccines) was observed, which continued to 4 months.	
3.C.2	Field studies	Field studies have been performed in cattle and pigs in outbreak situations using commercial batches of vaccine.	*Additional information*
3.D	Assessment reports.		
3.E.2	Post-marketing pharmacovigilance.	A summary of adverse events from surveillance of the BIAH water-in-oil-in-water oil emulsion vaccines distributed worldwide have been provided. Adverse events are consistent with the SPC and package leaflet.	*Assured*

Production & Distribution data requirements for the PEF

Chapter 4	Production and distribution data	Prequalification evidence to support PQV listing	PQv standards
4.1	Provide information on the quantity of finished product distributed domestically and exported in the previous 3 years.	Information on the number of doses supplied as finished product both domestically and internationally provided for the years 2015 - 2022.	*Assured*

4.2	Provide a list of countries where the product is licensed (marketing authorization) and supplied.	As of 2023, the product AFTOPOR or AFTOPOR DOE has a marketing authorization or is authorized for import in 17 countries: Australia, France, Germany, Hong-Kong, Indonesia, Iran, Israel, Japan, Lebanon, Malaysia, New Zealand, South Korea, Taiwan, Thailand, UK, USA and Vietnam.	*Assured*

Update on regulatory actions data requirements for the PEF

Chapter 5	Update on regulatory actions	Prequalification evidence to support PQV listing	PQv standards
5.1	Provide information on post-authorization regulatory actions.	The manufacturer has confirmed that no refusals, suspensions or withdrawals were made as post-authorisation actions for AFTOPOR vaccine.	*Assured*
5.2	Provide a list of lots rejected by the NRA, if applicable.	The manufacturer confirmed that no final FMD vaccine batch/lots had been rejected by a supervisory authority for release of the product.	*Assured*
5.3	Describe restrictions on distribution or recalls, including manufacturer-initiated recalls.	The manufacturer confirmed that no restrictions on distribution or recalls, including manufacturer-initiated recalls.	*Assured*
5.4	Name clinical trial suspensions, including manufacturer-initiated suspensions.	The manufacturer confirmed that there have been no clinical trial suspensions, including manufacturer-initiated suspensions.	*Assured*
5.5	Describe dosage or schedule modifications since the initial marketing authorization/product was granted.	The manufacturer confirmed that there have been no dosage or schedule modifications since the initial MA was granted.	*Assured*
5.6	Provide information on changes in target populations or indications since the initial marketing authorization/product was granted.	The reference MA has been regularly varied to include new strains of FMD as part of the multi-strain dossier approach.	*Assured*

5.7	List the GMP and/or Biosafety/Biosecurity inspections conducted by NRAs within the previous 3 years, including the scope of each inspection.	The manufacturer provided a list of GMP and Biosafety/Biosecurity inspections conducted by NRAs within the previous 3 years. Further information on the scope of the inspections is included in Part 1.	*Assured*
5.8	List inspections conducted by foreign GMP and/or Biosafety/Biosecurity authorities within the previous 3 years, including the scope of each inspection.	The applicant advised that foreign inspectors regularly visit the company's different manufacturing facilities. No information is provided on the scope of such inspector visits.	*Assured*

Provision of sera from batch release potency tests data requirements for the PEF

6.	Provision of sera from batch release potency tests	Prequalification evidence to support PQV listing	PQv standards
	Manufacturers with PQv listed FMD vaccines should commit to provide sera from batch release potency tests to independent laboratories once the terms for supply and testing have been agreed with stakeholders and published on the PQv website.	No general commitment to provide sera from batch release potency tests to independent laboratories has been made. The applicant points out that sera are already provided to internationally recognized reference laboratories by mutual consent.	*Additional information*