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
DECIVAC FMD DOE

Manufacturer/Applicant
MSD Animal Health

Prequalification number
PQv22-003

Date adopted by the SCPQv
12 April 2024

Date added to the list of prequalified FMD vaccines (PQv list):
16 April 2024

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 (PSR) for **DECIVAC FMD DOE**, manufactured by **MSD 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 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 NRA(s) 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 **31 August 2023**, the applicant **MSD Animal Health** submitted an application for prequalification for **DECIVAC FMD DOE**.

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 SCPQv reviewed the evaluation report at its meeting on 27 February 2024 and adopted the vaccine for PQv Listing on **12 April 2024**, following responses to arising queries.

The vaccine is indicated for **cattle, sheep, pigs and goats** against **FMD serotypes O, A, Asia 1 and SAT 1 (multistrain vaccine with between 1 and 3 strains per dose).**

The route of administration is **intramuscular or subcutaneous in ruminants, intramuscular in pigs.**

The vaccine is a **double oil emulsion (DOE) vaccine adjuvanted with Montanide ISA 206.**

The primary vaccination schedule is **two doses 3 to 5 weeks apart**.

A booster dose is recommended **every six months.**

The vaccine is manufactured by **MSD Animal Health** in conformity to the principles of EU Good Manufacturing Practice (GMP) as certified by the national regulatory authority for GMP **LANUV [Landesamt für Natur, Umwelt und Verbraucherschutz NRW, Germany) for Intervet International GmbH, site in Köln, Germany and the Medicines Evaluation Board – Veterinary Medicinal Products Unit, The Netherlands for Intervet International B.V. in Boxmeer, the Netherlands.**

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: **LANUV, Veterinary office of Cologne, and the Friedrich Loeffler Institute (FLI)**

Address of manufacturing site(s):
Antigen production, formulation, filling, packaging and QC testing take place at:
Intervet International GmbH
Osterather Str. 1a
50793 Köln, Germany

Centrifugation of inactivated FMD antigen may also take place at:
Intervet International B.V.
Wim de Körverstraat 35
5831 AN Boxmeer
The Netherlands

Annex 1. Summary of evidence provided to support PQv Listing for DECIVAC FMD DOE

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 Guideline.
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 Guideline. 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 Guideline. 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
GERMANY *	BFA V/MKS/2/ 2000, 31 Jul 2000	
The NETHERLANDS*	REG NL 116656, 22 May 2018	
ALGERIA		
KUWAIT		
LEBANON		
PAKISTAN		
SOUTH KOREA		
THAILAND		
TURKEY		

* The vaccine covered by this PQv listing is the same as that for which national multistrain marketing authorizations have been issued in these two countries. Due to the different epidemiological situation between countries, the strains of FMD virus that are included within the scope of national authorizations, including multistrain authorizations, differs between countries. Likewise, authorizations may differ in terms of the approved minimum potency per strain (usually 3 vs. 6 PD_{50}). This PQv listing includes all strains for which the manufacturer has demonstrated compliance with the technical requirements described in this report (particularly with respect to a minimum potency of 6 PD_{50}), irrespective of the national authorization on which the strains are included.

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 2025 (Germany) and 2026 (Netherlands).	*Assured*
	NRA for GMP	LANUV (Landesamt für Natur, Umwelt und Verbraucherschutz NRW, Germany)	
1.A.1	Biosafety & Biosecurity	Last inspection 11 May 2023. The license from the LANUV is valid unlimited.	*Assured*
	Health and Safety Executive	LANUV, Veterinary office of Cologne, Friedrich Loeffler Institute (FLI).	
1.B	Summary Product Characteristics (SPC)	A SPC following the format of the EU QRD text (v8.2) was provided. Label claims are supported by safety and efficacy studies that comply with the WOAH standards for FMD.	*Assured*
1.C	Labelling and package insert	Labels and package insert were provided. Information on product label includes the following sections: name of product, dose, volume, route of administration, withdrawal period, batch no., expiry date, MA number, and on the 100 and 250 ml bottles also pharmaceutical form, target species, special warnings, storage, and address of manufacturer.	*Assured*
1.D.	Lot summary protocol	Final batch protocols representative of batch of vaccine released for supply were provided (more than 3 monovalent, 3 bivalent and 3 trivalent vaccine batches)	*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, expressed as per dose of 2 ml provided. One dose of 2 mL of DECIVAC contains between one and three antigens (>6 PD_{50}/strain) in a double oil emulsion (DOE) adjuvant.	*Assured*
2.B	Method of Manufacture		
2.B.1	Description of manufacturing process	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 are carried out on each batch of viral culture and a check of residual live virus is performed. Certificates of analysis which include test specifications and test results have been provided for more than 3 monovalent and 3 trivalent vaccine batches. All tests were within the defined specifications and the batch results support consistency of production.	*Assured*

2.B.1.a	Validation of the inactivation process	The cultured FMD virus is clarified by an appropriate method and the viral harvest inactivated by the addition of binary ethyleneimine (BEI). After adding the inactivant, the batch of virus is transferred to second sterile vessel where inactivation is completed. The inactivation kinetics is validated for the time period for chemical treatment and temperature at industrial scale with the manufacturing equipment used for routine production. The inactivation procedure was shown to be satisfactory with a decrease in virus titre, when plotted logarithmically, that was linear, and extrapolation indicated that there is less than 1 infectious virus unit per 10,000 L of liquid preparation at the end of inactivation. During the inactivation of each manufactured batch, the virus titre is monitored by a sensitive and reproducible technique using a sensitive cell line to monitor the inactivation kinetics. After inactivation, any residual BEI in the harvest is chemically neutralized.	*Assured*
2.B.2	Detailed flowcharts	A detailed flow chart of the production steps of Decivac FMD DOE was provided from the Master Seed Virus (MSV) to filling and labelling of the finished product. The flow chart included the in process (IP) and final product (FP) Quality Control (QC) tests.	
2.C	Production and Control of Starting Materials		
2.C.1	Starting materials of biological origin		

2.C.1.1	Virus seed	For each virus strain(s) that may be/is included in the vaccine, the source of the isolate has been recorded including details of the country of origin, species, and date of isolation, type of material from which virus was isolated. The in vitro passage history of each vaccine strain has been recorded, including details of the ingredients used and any adaptation to growth on a cell line. Details of the preparation and passage of the Master Seed Virus (MSV) and Working Seed Virus (WSV) and storage conditions (≤ –70°C) were provided as evidence. Tests results for the MSV tested in accordance with EU (Ph. Eur.) requirements (identity, titration, absence of bacteria and fungi (sterility test), absence of mycoplasmas and absence of extraneous agents) were provided as evidence. A BSE/TSE risk assessment is included with details on the measures taken to minimize the risk of Transmissible spongiform encephalopathies.	*Assured*
2.C.1.2	Cell seed	The Master cell bank is controlled for identity, karyotype, sterility, absence of mycoplasma and absence of extraneous agents.	*Additional information*
2.D	In-Process Controls		
2.D	In-process controls	***Inactivation kinetics.*** The inactivation kinetics is monitored during the inactivation step and is compliant with chapter 3.1.8 WOAH Terrestrial Manual. The decrease in virus titre, plotted logarithmically, is linear and extrapolation	*Assured*

		indicates that there is less than 1 infectious virus unit per 10,000 L of liquid preparation at the end of inactivation. **Inactivation control (innocuity test/absence of residual live virus).** The inactivation control is performed after viral inactivation of the bulk antigen. The Inactivation test method using virus titre is sensitive and reproducible. An antigen sample representing at least 200 doses of vaccine is used for testing for freedom of infectious virus by inoculation of sensitive cell culture monolayers. The method and validation report were provided. ***Residues of inactivating agents.*** The test is performed before release of each lot of inactivated harvest bulk antigen. The method and validation report were provided. ***FMDV antigen identity and purity test*** Identity and purity are controlled by ELISA on inactivated purified bulk antigen. The method and validation report were provided. ***FMDV antigen mass (146S) content*** The 146S antigen content of each batch of bulk inactivated antigen is determined by density gradient centrifugation and ultraviolet spectrophotometry. The specification set for release is such that a batch of	

		antigen produced according to the authorized manufacturing process contains a sufficient amount of 146S inactivated FMDV to formulate potent vaccines. The method and validation report were provided.	
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 brief description of the final product identity test performed on each batch of manufactured vaccine was provided. Validation reports for the identity of each vaccine serotype provided.	*Assured*
2.E.3	Batch potency	Description of the final product batch potency test and validation reports for the potency test that established the VN Ab titre specifications for release of 6 PD_{50}/dose vaccine were provided. Evidence was presented of at least one PD_{50} (50 per cent cattle protective doses) challenge test per vaccine strain to establish efficacy in cattle, and demonstrating the vaccine contains at least 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 stability/type and viscosity.	*Additional information*
2.E.5	Identification and assay of excipients components		*Not required*

2.E.6	Safety tests	Routine target animals batch safety tests are not performed by the manufacturer in compliance with the standards of the WOAH Terrestrial manual, Ph. Eur. 0063 and VICH GL50.	*Additional information*
2.E7	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	During the manufacturing process, purification steps are included to remove foot-and-mouth disease viral NSPs and other impurities. Purity Testing (freedom from NSP) not performed as a routine FP test as the vaccine has been shown in registration studies not to stimulate antibodies to NSPs and consistency of production has been adequately demonstrated.	*Assured*
2.E.9	Inactivation test	Inactivation test is performed on the bulk antigen and so is not required to be repeated on FP in line with EU requirements.	*Assured*
2.F	Batch consistency		
2.F	Batch consistency – Process validation.	Batch protocols for three monovalent and three trivalent vaccine batches outlining all the production steps, specifications and results for all tests performed during the production process and on the finished product provided and show consistency of manufacture	*Assured*
2.G	Stability		
2.G	Stability	Stability of 3 batches tested regularly over the claimed	*Assured*

		shelf life provided and shown to be at least 12 months. The stability study demonstrates that the results of the vaccine remain within the specifications for physicochemical, microbial and immunogenic parameters during at least 12 months of storage at 2-8°C.	

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, goat and pig provided. The safety studies were conducted to the standards of International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) and were in accordance with the principles of Good Laboratory Practice (GLP). VICH safety studies were conducted with a single/double dose and repeat dose. The safety studies were performed with vaccines formulated to contain the maximum permitted payload and number of antigens. The safety warnings on the SPC/label/package insert reflect the local and systemic reactions observed in the safety studies. Pregnant/lactating animals can be vaccinated. Laboratory safety data in lactating cows have been provided. Furthermore, field usage indicates that the vaccine is safe in these categories.	Assured

		No specific studied have been conducted to investigate the interactions with other veterinary medicinal products given at the same time as the vaccine.	
3.B.2	Field studies	Evidence was provided for field trials conducted to demonstrate the safety of DECIVAC FMD DOE under field conditions.	Additional information
3.B.4	User safety	Users of the vaccine are informed of the safety risk associated with vaccines adjuvanted with mineral oil, with the information described in the package insert accompanying the product.	Additional information
3.B.5	Consumer safety	Withdrawal period for meat and milk is zero days for DECIVAC FMD DOE administered to food producing species.	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 per cent cattle protective doses) challenge test was performed using each vaccine strain to establish efficacy in cattle, and demonstrating the vaccine contains at least 6 PD_{50}. In animals free from antibodies to FMD, the onset of immunity was established using serological data. A single dose primary vaccination provided protection as determined by serology within 10 days of vaccination. The duration of immunity was demonstrated by serology. In cattle free from antibodies to FMD receiving one vaccination, a serological response with antibody levels superior to the protective thresholds persist for at least one year. In areas where FMD is endemic, or in animals with MDA,	*Assured*

		administration of the second injection of the primary vaccination schedule is strongly recommended. The efficacy was shown in 2-4 months old pigs vaccinated with one dose (2 mL) of vaccine against challenge performed 4 weeks post vaccination with O1 Manisa, Asia 1 Shamir and A22 Iraq strains. The O1 Manisa vaccine strain provided in pigs protection against a challenge with O Taiwan FMDV. For sheep and goats, serological results were provided to support the efficacy of the vaccine which show that virus neutralizing VN-Ab titres are similar as titres in cattle that provide protection after challenge. The chapter 3.1.8 Terrestrial Manual considers that a successful test in cattle is considered to be sufficient evidence of the quality of a vaccine to endorse its use in other species. Therefore, potency results from a cattle test are considered to be a reliable indicator of vaccine quality and the extrapolation to sheep, goats and pigs is acceptable. The manufacturer has provided data to support DIVA claims.	
3.C.2	Field studies	Field trials for the evaluation of efficacy under field conditions were not performed in the EU because vaccination against FMD is prohibited. A publication shows the efficacy of the vaccination with Decivac FMD DOE after an outbreak of foot-and-mouth disease caused by serotype O virus in cattle and pigs in South Korea in 2010-2011.	*Additional information*
3.D	Assessment reports.		

3.E.2	Post-marketing pharmacovigilance	Periodic safety and efficacy update reports (PSUR) are provided for the period between 2004 and 2017. The reports are consistent with the potential adverse reactions on the SPC.	*Assured*

Production & Distribution data requirements for the PEF

Chapter 4	Production and distribution data	Prequalification evidence to support PQV listing	PQv standards
4.A	Provide information on the quantity of finished product distributed domestically and exported in the previous 3 years.	Information on batches of FMD vaccine supplied as finished product both domestically and internationally is provided.	*Assured*
4.B	Provide a list of countries where the product is licensed (marketing authorization) and supplied.	The vaccine is licensed in 9 different countries: Germany, the Netherlands, Algeria, South Korea, Kuwait, Lebanon, Pakistan, Thailand and Turkey.	*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.A	Provide information on post-authorization regulatory actions.	The manufacturer confirmed that no regulatory actions had been taken by any NRA where the product is authorized/registered.	*Assured*
5.B	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.C	Describe restrictions on distribution or recalls, including manufacturer-initiated recalls.	The manufacturer confirmed that there have been no recalls for Decivac FMD DOE, including manufacturer-initiated recalls.	*Assured*
5.D	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.E	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.F	Provide information on changes in target populations or indications since the initial marketing authorization/product was granted.	Since the first authorization, no additional target species has been added to the authorization.	*Assured*
5.G	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 inspections conducted by the NRA for GMP and Biosafety/Biosecurity within the previous 3 years.	*Assured*
5.H	List inspections conducted by foreign GMP and/or Biosafety/Biosecurity authorities within the previous 3 years, including the scope of each inspection.	The manufacturer provided a list of inspections conducted by GMP authorities within the previous 3 years, including the scope of each inspection.	*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.	A commitment to provide sera from batch potency tests was provided.	*Additional information*