International standards and frameworks for high-quality FMD vaccines from a regulator's perspective

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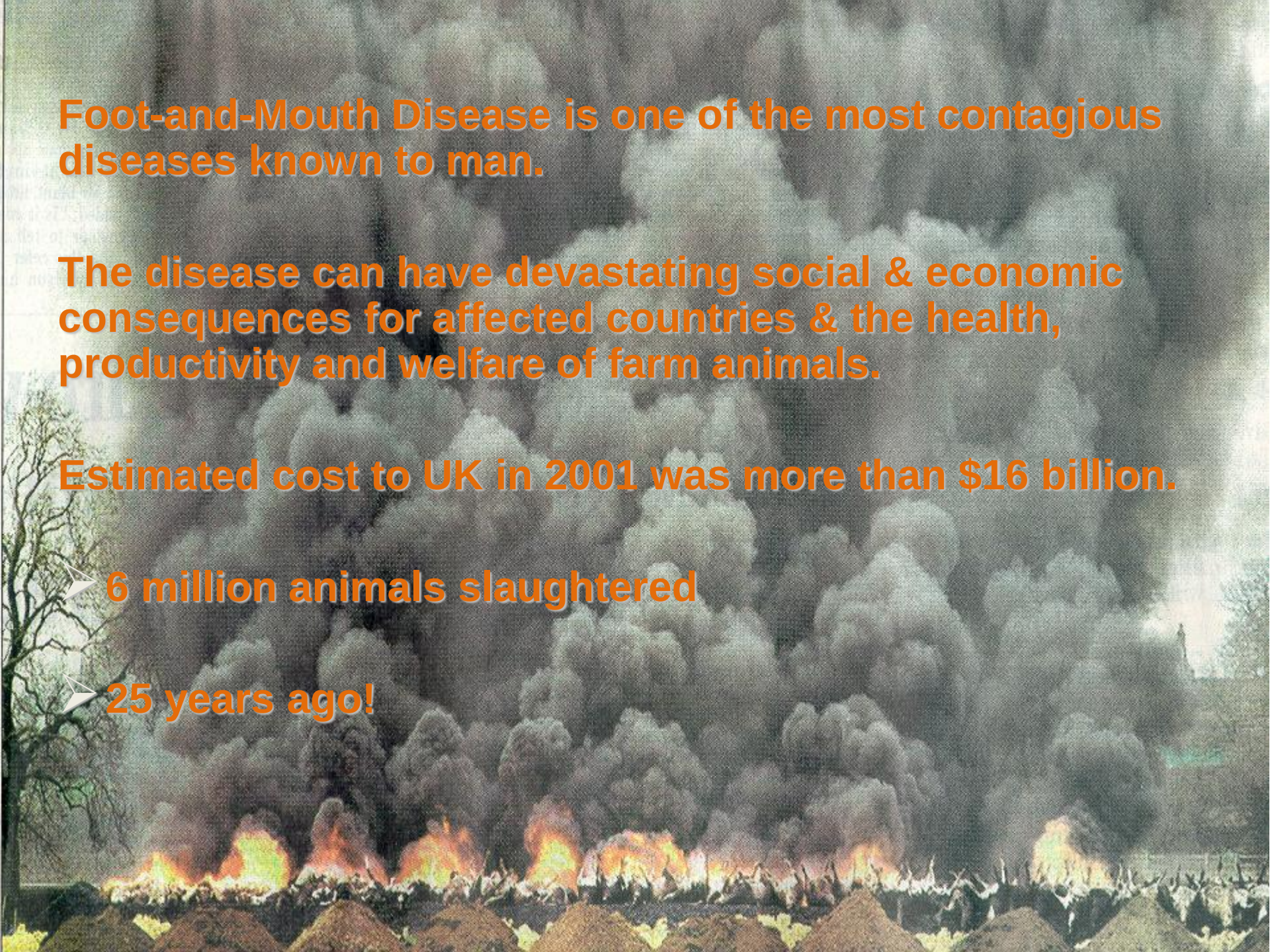


Foot-and-Mouth Disease is one of the most contagious diseases known to man.

The disease can have devastating social & economic consequences for affected countries & the health, productivity and welfare of farm animals.

Estimated cost to UK in 2001 was more than $16 billion.

- 6 million animals slaughtered
- 25 years ago!

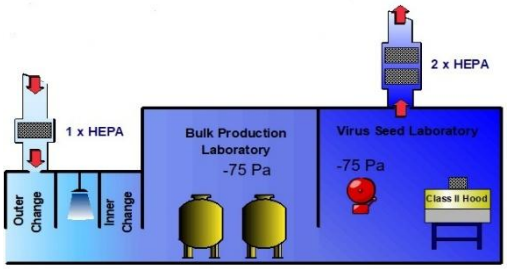
International standards and frameworks for high-quality FMD vaccines from a regulator's perspective

1. Introduction to the regulation of FMD vaccines
2. The role of a regulator in granting a product licence for an FMD vaccine
3. Introduction WOAH and the European Pharmacopoeia standards
4. 3Rs developments that facilitate batch release of FMD vaccines
5. Examples of the challenges in evaluating FMD vaccines to WOAH standards
6. Quality Verification System (QVS) or Pre-Qualification scheme (PQv)

FMD vaccines are probably the most regulated vaccines globally

Minimum Biorisk Management Standards for FMD labs

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

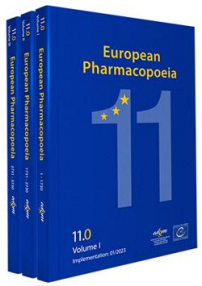


Biosecurity standards. National & Regional legislation & standards BSL3, SAPO4

FMD vaccine Marketing Authorisations, Product & Emergency Licences

QC, tests & surveillance

WOAH/FAO Foot-and-Mouth Disease Reference Laboratories Network



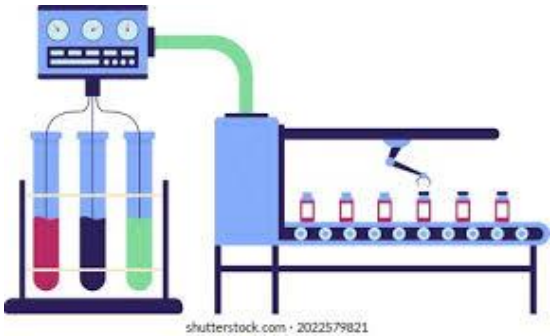
World Organisation for Animal Health | CODES AND MANUALS

National, Regional Pharmacopoeia standards and/or WOAH standards

Strict distribution (GDP) & administration controls

Good Manufacturing Practice (GMP). Regional & National)

Inspections



WOAH Terrestrial Code and Manual standards for FMD

FMD Vaccine standards for manufacture

FMD Vaccine standards for safety testing

FMD Vaccine standards for efficacy

Standards for Diagnostic tests

Standards for disease surveillance

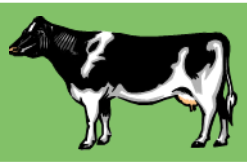
Standards for slaughter and carcass disposal

Risk mitigation for animal products

Standards for zoning & compartmentalization

Development of a new FMD vaccine strain can take 6 -18 months even before the safety & efficacy studies (including potency) are initiated

Collection of field samples from infected animals



FMD regional/world reference lab

Identification PCR/VNT/ELISA & official designation of Isolate

Manufacturer requests isolate for developing new FMD vaccine strain

QC Laboratory

- Characterisation with existing vaccine strains by VNT
- Replication rate in production (BHK) and QC test cells
- Regulatory Reports

Production Unit

1. Production yield
2. Replication rate
3. Stability
4. Inactivation data
5. QA documentation

FINAL PRODUCT SPECIFICATIONS
Antigenic payload & potency

Risks for FMD vaccine usage

- HIGH COSTS for development
- TIMELINES for submission of dossier extended
- DELAYS in batch release re-testing

- LOW COSTS
- RAPID Authorisation
- RAPID batch release

LOW RISK

Optimum regulation for FMD outbreak?

HIGH RISK

?

- Full Product Licence
- Satisfactory data for Q, S & E for each antigen
- Full compliance with Ph.Eur & WOAH standards
- GMP site inspection & Certification
- Official control of batches by State/Reference lab

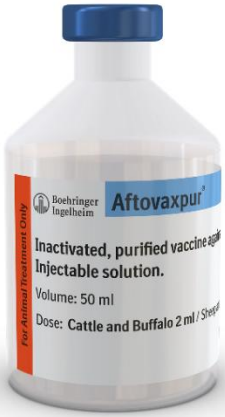
- Emergency authorisation/use
- Limited data on Q, S & E
- WOAH/Ph.Eur standards?
- GMP site inspection?
- State laboratory re-testing?

Regional and International Regulatory Standards have risen over time to provide more confidence in the quality, safety and efficacy of veterinary vaccines, but with them comes the associated increase in costs, timelines and data requirements

- A regulator for FMD vaccine registration is required to establish that the vaccine complies with national legislation and **meets the MINIMUM standards** of the applicable Pharmacopoeia, e.g. Ph.Eur
- That the **BENEFITS outweigh the RISKS** for the vaccine
- And that the **indications and claims are supported** with robust data for each target species listed on the label & Product Information sheet
- A regulator does NOT assess whether a particular FMD vaccine will be effective at controlling an outbreak in a particular country or region:
  - *Most applications only include data on homologous challenges*
  - *Reference laboratories perform vaccine matching studies*
  - *Reference laboratories may make vaccine recommendations via tools such as PRAGMATIST (https://www.fao.org/eufmd/tools/pragmatist/en/)*
  - *Reference laboratories will NOT certify vaccines for tenders*

So do they do exactly what they say on the bottle?

It can be challenging for veterinary authorities procuring FMD vaccines to ensure they select the right product for their particular needs



WOAH standards for FMD vaccine production & testing

- WOAH develops and publishes:
  - *Health standards for trade in animals & animal products*
  - *Biological standards for diagnostics & veterinary vaccines*
- Adopted at the General Session by Member Countries
- **WOAH Terrestrial Manual**:
  - Part 1 General standards e.g., Principles of vaccine production (1.1.8)
  - Part 2. Specific recommendations e.g. Minimum requirements for the production and quality control of vaccines (2.3.4)
- **Part 3. Listed Disease Chapters e.g. FMD (3.1.8)**
  - Part A: INTRODUCTION overview of tests and vaccines
  - Part B: DIAGNOSTIC TECHNIQUES (test methods for FMD)
  - Part C: REQUIREMENTS FOR VACCINES (General GLs)

Council of Europe & European Pharmacopoeia

- The Ph. Eur convention, 40 members, & more than 30 observers
  - ***Ph. Eur. texts are MANDATORY*** *(**legally binding**) to ensure harmonisation of standards for the authorisation & manufacture of medicinal products*
  - *Product-specific monographs (e.g. FMD 0063) must be read in conjunction with the General Monographs (e.g. Veterinary Vaccine 0062) & General texts (e.g. Efficacy 5.2.7)*
  - *ALL BATCHES of the product must pass or be capable of passing the tests specified in the TESTS section of the monograph until the end of its shelf-life.*
  - ***It is not necessary to use the test method described*** *in the monograph as long as assurance that the product complies can be obtained by an alternative validated method*
  - *The efficacy requirements have to be addressed but the methods described are not legally binding, e.g. for FMD* 'tests immunogenicity (section 2-4-2) may be used during the demonstration of efficacy. The manufacturer can justify the approach used to support the claims

- 3Rs implementation in regulation is impacting batch release testing
  - *The European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, adopted by Ph. Eur*
  - *In the EU, animal usage for QC tests for medicinal products has declined by 39.% between 2018 & 2022 (942K to 571K). Batch potency 75% of QC tests*
  - *Non-animal tests should be used wherever possible* **5.2.14 Substitution of in vivo method(s) by in vitro Methods(s) for the QC of vaccines**
  - *Removal of In Process & final product tests e.g. target animal batch safety test (TABST)*
  - *Consistency of production* under robust quality systems
- **3Rs applied to Ph.Eur FMD testing**
  - **Immunogenicity Test**. The PD50/PPG test for **EACH FMD vaccine strain ONCE**
  - **Batch potency**. The PD50/PPG no longer performed & the described serological test may be replaced by *in vitro methodology*
  - *For many veterinary vaccines including some FMD vaccines, animals are no longer used in for QC batch release tests.*

Challenges assessing the quality of FMD vaccines to WOAH Standards

- Flexibility in their application & the absence of Mandatory requirements
- Part 3 Part C (e.g. FMD 3.1.8) The information concerning production and control of vaccines is given as an example; '***it is not always necessary to follow these when there are scientifically justifiable reasons for using alternative approaches*'.**
  - Good Manufacturing Practice (GMP) standards for production
  - Requirements for pharmaceutical quality
  - Requirements for safety testing
  - Requirements for efficacy testing

Good Manufacturing Practice (GMP) standards for production

- Only a very few veterinary authorities belong to PIC/S (Pharmaceutical Inspection Co-operation Scheme)
- GMP standards are primarily focused on National legislation, where the requirements may not be clear, e.g. Australia TGA (PIC/S) vs APVMA
- There are no specific WOAH International standards for GMP or WOAH GMP Inspectors:
  - Chapter: 1.1.8. Principles of vaccine production
  - Chapter: 2.3.2. Minimum requirements for the organisation and management of a vaccine manufacturing facility
  - Chapter: 2.3.3. Minimum requirements for the production and quality control of vaccines

Requirements for Quality

Examples of the absence of clarity on WOAH standards

WOAH 3.8 FMD, 5.6 Stability. *The stability of all vaccines, including oil emulsion vaccines, should be demonstrated as part of the shelf-life determination studies for authorisation. The shelf life of conventional FMD vaccines is usually 1–2 years at 2–8°C. Vaccines should never be frozen or stored above the target temperature*

Stability should be tested using the same methods described in Efficacy (C.5.3), but vaccinating the animals at the end of the shelf life of the product

Ph.Eur. 2-2-3 Stability This evidence takes the form of the results of potency tests carried out at regular intervals until 3 months beyond the end of shelf life on not fewer than 3 representative batches of vaccine kept under recommended storage together with results from studies of physical tests on the adjuvant, chemical tests on substances such as the adjuvant constituents and preservatives, and pH

Requirements for pharmaceutical quality testing

Examples of the absence of clarity on WOAH standards

WOAH 3.8 FMD, 3.1.8. In emergency situations where there is insufficient time to complete full testing of the MSV, provisional acceptance of the new strain should be based on a risk analysis of the possibility of contamination of the antigen produced from the new MSV with extraneous agents (It's treated with BEI?)

Example of unnecessary tests

WOAH 3.8 FMD, 3.1.8. 4.1 Innocuity testing. The **bulk inactivated antigen and the final formulated product** should undergo innocuity test to prove absence of infectious virus. In the final product, antigen must be extracted from adjuvant following an appropriate validated method.

Ph.Eur 0063. Only one innocuity test (residual live virus) on a proportion of each batch of bulk inactivated antigen

Requirements for pharmaceutical quality testing cont.

Example of an unnecessary batch release test

WOAH 3.8 FMD, 3.1.8. 4.5 Safety Testing. The safety of the final product should be proven batch to batch. The safety testing is conducted to detect any abnormal local or systemic adverse reactions.

Ph.Eur FMD 0063. The Target Animal Batch Safety Test has been removed

Examples of the absence of clarity on WOAH standards

WOAH 3.8 FMD, 3.1.8. 4.6 Potency Testing. The potency testing standard is the vaccination challenge test. However, indirect tests can also be used for *practicability and animal welfare considerations*, as long as correlation has been validated to expectancy of protection in the target animal

WOAH 3.8 FMD, 3.1.8. 4.4 Final product test. Products claiming to be purified from NSPs have to demonstrate their level of purification. Lack of reactivity has to be demonstrated in the final product

Requirements for safety testing

WOAH 3.8 FMD, 3.1.8. 5.2 Safety Testing. For the purposes of gaining regulatory approval, a trial batch of vaccine should be tested for local and systemic toxicity. . **Double dose** (e.g. two injections) and repeat single dose (after 14 days) tests using vaccines formulated to contain the maximum permitted payload and number of antigens are recommended to be conducted. In total, animals receive three injections

Ph.Eur & VICHGL44. No requirement for a double dose. And target animals should receive the **primary vaccination schedule plus a booster dose**.

Requirements for efficacy testing

WOAH 3.8 FMD, 3.1.8. 5.3 Efficacy Testing. Vaccine efficacy is estimated in vaccinated animals directly, by evaluating their resistance to live virus challenge or indirectly through in vitro testing using well-established correlations.

WOAH 3.8 FMD, 3.1.8. 5.3.4 Efficacy Testing. Efficacy tests in other target species, such as sheep, goats, pigs or buffalo are either different or not yet standardised**. In general, a successful test in cattle is considered to be sufficient evidence of the quality of a vaccine to endorse its use in other species.**

Ph. Eur Efficacy 5.2.7. Efficacy shall be demonstrated for each category of target animal species in which its use is recommended, by each recommended route and method of administration and using the proposed schedule of administration. Unless otherwise justified, the OOI & DOI shall be established

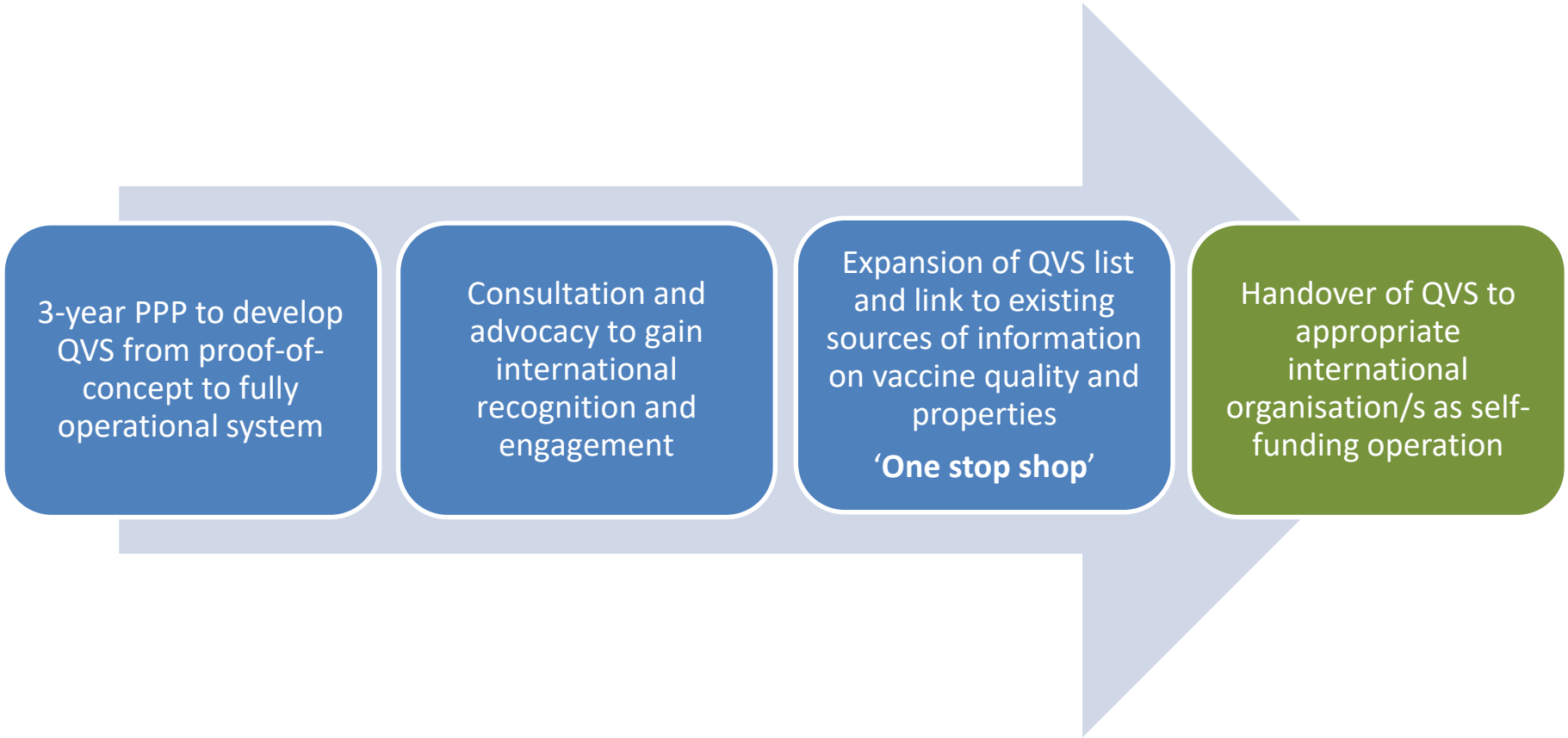
A Quality Verification System (QVS) for FMD vaccines (PQv)

- A procedure developed by EuFMD for **independent peer review of** FMD vaccines to confirm compliance with **minimum internationally accepted standards of the WOAH Terrestrial Manual**
- **The Standing Committee on Pre-qualification (SCPQv)** made up of recognised experts in the field of FMD, vaccinology, GMP, biosecurity & regulatory affairs, reviews **applications from manufacturers** & **publishes evaluation reports & product information**

A Quality Verification System QVS for FMD vaccines

- **For Manufacturers:**
- QVS provides a procedure for independent international review of the quality of a vaccine with inclusion of qualified vaccines in a published FAO list.
- **For Purchasers and users**
- Independent advice for contingency planning by risk managers
- Reduces the time and work required by procurement managers, **removing the need to evaluate 'quality' as part of the procurement process.**
- QVS ensures that the properties and claims for the vaccine are fully supported;
- It remains the responsibility of the risk/procurement manager to ensure that the vaccine is appropriate for use in a particular epidemiological situation (**fitness-for-purpose**)
- EuFMD QVS FAO webpage

Steps in the development of a QVS for FMD vaccines



Stage 1

2020–2024 Proof-of-concept by EuFMD

- Mandate and funding from EuFMD Commission
- PQv system established based on assuring quality through documentary review
- Voluntary submission of applications from manufacturers evaluated free of charge
- QVS/PQv list published on EuFMD webpage as information resource for risk managers

Stage 2

2026–2028 Fully operational system developed jointly by EuFMD and external funder(s)

- Operational and funding model in line with FAO framework for public private partnerships
- Advocacy and consultation with stakeholders to raise profile and gain international acceptance of PQv
- Extend scope to include independent QC testing of vaccines and assurance of GMP
- Develop a model for sustainable operation of PQv based on cost recovery

Stage 3

2028+ Sustainable long-term operation as a self-standing entity

- Transition to operating as a self-sustaining and independent entity linked to a suitable host organization
- QVS list is internationally recognized as a reliable badge of quality
- Option to extend scheme to include other veterinary vaccines and other essential veterinary medicines

Thank You

Any Questions?

David Mackay is acknowledged for leading the development of the QVS and providing comments

Passive Immunisation

Friedrich Loeffler & Robert Koch

1897 discovery of FMD