Official Control of FMD Vaccines

Dr David Mackay

Consultant on vaccine security to EuFMD

EuFMD. European Commission for the Control of Foot-and-Mouth Disease

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- Overview of testing
- Principles of official control
- Official batch release and independent testing
- Parameters for testing FMD vaccines
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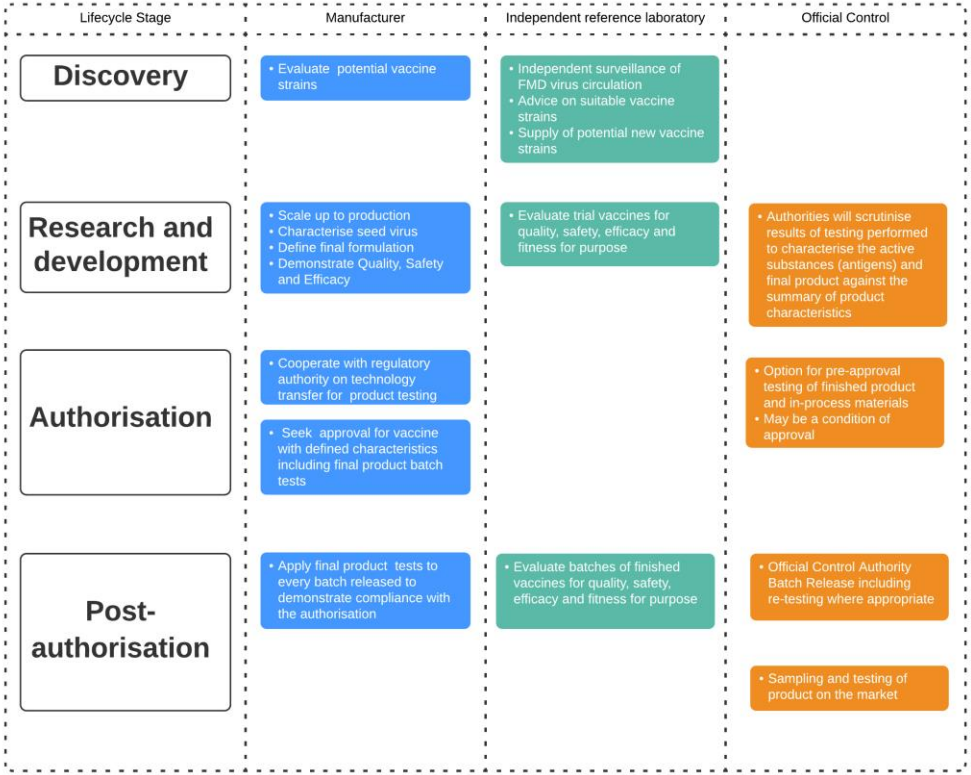
Overview of testing applied during the lifecycle of a FMD vaccine



Official control of FMD vaccines – principles

- **Quality has to be 'built in'** to a vaccine and cannot be evaluated by re-testing alone
- Production of high quality vaccine relies on
  - Inspection and approval of **site of manufacture** to ensure compliance with GMP
  - Assessment and approval of a dossier describing the **manufacture and control** applied with respect to **pharmaceutical quality, safety & efficacy**
  - **Post-approval monitoring** by batch release, pharmacovigilance, sampling and testing
- Reliance placed on re-testing of the finished product varies between different countries and regions depending on the **policy applied** (routine, random, targeted, risk-based, or no re-testing)
- Vaccines against epizootic diseases such as FMD are normally subject to **batch release** by the National Regulatory Authority (NRA), often involving re-testing, particularly when vaccination is part of an official control or eradication policy

Official batch release of FMD vaccines

- Confirmation by a national regulatory authority (NRA) that a batch of vaccine complies with the **specifications described in the approved registration dossier** /licence / marketing authorisation before its release onto the market
- Official Control Authority Batch Release (EU)/Serial Release (USA) relies on a combination of
  - **review of documents** prepared by the manufacturer for the batch of vaccine to be released
  - **targeted retesting** by an Official Medicines Control Laboratory (OMCL) i.e. a laboratory officially approved by the NRA to carry out the testing required to the relevant quality standard

Independent testing of FMD vaccines

- Distinction between
  - **official control** under the authority of the NRA

  and
  - **independent testing** carried out by an laboratory on behalf of a customer (who may be a government, international organisation, NGO, regulatory authority, private company or the manufacturer) to verify the compliance of the vaccine with respect to international, or other, standards set by the customer, generally at least the minimum standards specified in the Manual of Manual of Diagnostic Tests and Vaccines for Terrestrial Animals for the World Organisation for Animal Health (the “OIE Manual”)

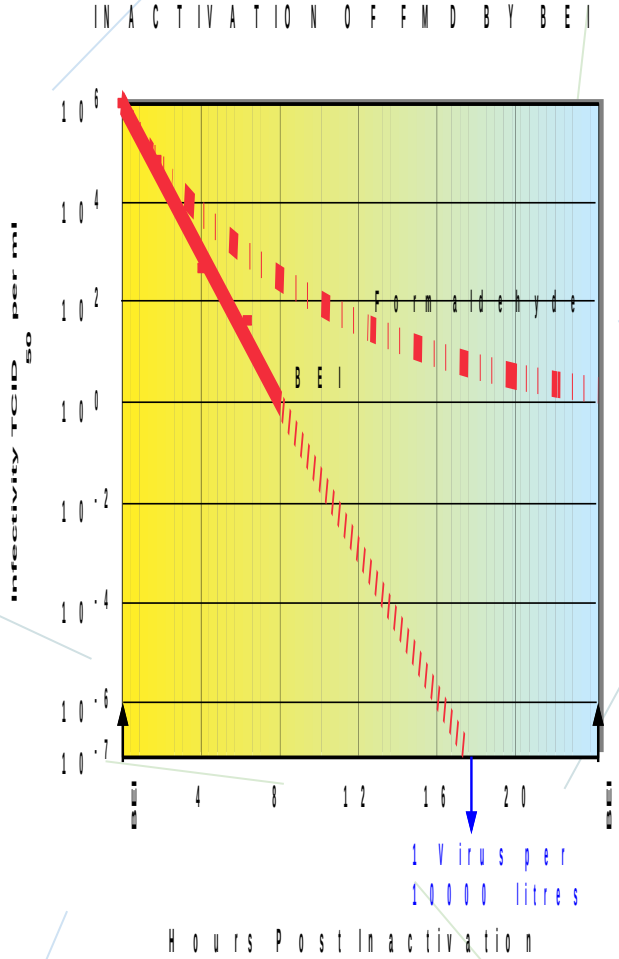
What are the key parameters to re-test?

- OIE Manual (Chapter 3.1.18 Section C.4 'Final product batch tests) specifies the following final product tests must be performed by the manufacturer
  - **Innocuity** (absence of live virus)
  - Sterility (absence of bacterial contamination)
  - Identity (virus(es) specified on the authorisation are present and no others)
  - Purity (freedom from non-structural proteins)
  - Safety (local and systemic reactions are within accepted limits)
  - **Potency** (immunogenic potential/ability to protect is at least the minimum level specified in the authorisation)
- Testing requires an appropriate level of biosecurity, particularly for innocuity and potency where the use of live virus is usually required

Innocuity of FMD vaccines

- Demonstrating innocuity is essential for FMD vaccines and is assured by
    1. Application of a **validated inactivation procedure** using a first order inactivant, usually the aziridine compound binary ethyleneimine (BEI)
    2. **Confirmation of kinetics** of inactivation for each batch of antigen with an acceptable end point (<1 infectious particle/10^4 litre)
    3. **Control of inactivation** for each batch of inactivated antigen prior to downstream processing
- Parameters 1-3 can be verified on the basis of documentary inspection

Inactivation of FMD antigens



Innocuity of FMD vaccines

- The OIE Manual specifies a test for innocuity of the final product involving elution of antigen
  - Authorities may not require this test provided that a test is performed on the bulk inactivated antigen and all other requirements for consistency of production have met
  - Adjuvants and excipients may interfere with the ability of cells to detect live virus requiring the development and validation of suitable techniques for each vaccine by the testing laboratory
  - Elution of antigen from the formulated product is technically challenging
  - Testing is often more reliable on the final concentrated, bulk inactivated antigen
  - Authorities can make it a condition of authorisation for manufacturers to supply both final product and bulk inactivated antigen for re-testing by official laboratories

Potency of FMD vaccines

- The definitive test for potency measures *in vivo* protection of cattle 21 days after vaccination against a standardized challenge
- Protocols are described in Chapter 3.1.8 Section C.5.3 'Efficacy' of the OIE Manual for determining potency (Number of 50% protective doses - PD_{50}, Protection against generalized infection - PGP)
- *In vitro* serological test may be accepted for the batch release potency test **provided** that a correlation has been shown between serological titre and protection and a cut-off defined that corresponds with a vaccine of the minimum potency defined in the authorisation (e.g. Expected Percentage of Protection – EPP)
- Challenge tests should be performed at least once for each strain as part of the testing for authorisation

Potency of FMD vaccines

- Unusually, challenge may be performed with the (homologous) vaccine virus
  - Demonstrates highest level of protection that can be expected
  - OIE Manual requires vaccines to contain at least 3 PD_{50}
  - 'Emergency' vaccines generally contain at least 6 PD_{50}
- Replicating the manufacturers batch potency test requires access to appropriate reference materials (viruses, standards and sera)
- Method transfer/cooperation with an official control laboratory can be made a requirement of approval

EuFMD/FAO proposal for pre-qualification of vaccines against FAST diseases

- EuFMD/FAO is developing a scheme for pre-qualification of vaccines against foot-and-mouth and similar transboundary (FAST) diseases
- Scientific peer review of an application describing manufacture and quality control of the vaccine to assess compliance with minimum international standards as defined in the OIE Manual
- Outcome will be inclusion of eligible products on a list of pre-qualified vaccines published on the EuFMD website
- Provides independent assurance on the quality, safety and efficacy of a vaccine and that the vaccine complies with the product literature and labelling
- Does not evaluate fitness-for-purpose for use in particular epidemiological situations; this has to be done by the customer at the time of tender

Key messages on re-testing of FMD vaccines

- **Official batch release**, including re-testing as appropriate, determines compliance with the authorisation/license/registration
- **Independent re-testing** determines compliance with international standards for the individual batch(es) tested
- Review of **batch documentation** can provide considerable information and assurance that appropriate standards have been met
- Re-testing of the key parameters of innocuity and potency can best be done through **cooperation with manufacturers**
- Re-testing can **supplement but not replace** the need to control the manufacture and quality control of FMD vaccines against the standards defined in the authorisation

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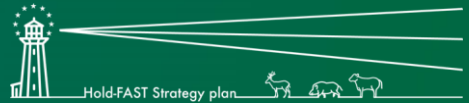

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