

**FOOT AND MOUTH DISEASE
Symposium**

17 – 18 March 2003

FMD Symposium Session I

Introduction

**Moderator: Dr K. De
Clercq**

09:00-12:00

Foot-and-mouth Disease Vaccine regulatory and scientific background

PETER CASTLE
Secretary to the
European Pharmacopoeia Commission

Topics

- Ph Eur monograph
- Relations with EU
- Relations with CVMP guideline
- Revision of Ph Eur monograph
- Objectives of the meeting

Ph Eur Castle17032003

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Ph Eur monograph

- Drafted late 1970s, now applicable in 30 countries
- Difficult consensus on potency test (PD₅₀ vs K-index, etc), minimum potency, safety test
- Covered available vaccines, adapted to current disease control strategy
- Intradermolingual safety test reflected concern over inactivation of FMD virus

Ph Eur Castle17032003

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Ph Eur monograph (2)

- Scope limited to ruminants
- Potency test in cattle
- No batch potency test cited
- Monograph (together with general monograph *Vaccines for Veterinary Use*) provided standard for compliance

Phar Codex 71032003

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Vaccines for veterinary use

- General requirements apply to FMD vaccine
- Requirements for purity of cells, seed lots, inactivation etc
- Guideline gives details of possible waivers for emergency use

Phar Codex 71032003

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Relations with EU

- Monograph only official standard
- Used by DGVI as basis for tenders
- DGVI observer in Group 15V proposed revision of monograph when EU control strategy changed
- EU allows emergency use of unauthorised vaccines but no waiver for compliance with monographs(s)

Phar Codex 71032003

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1990s revision

- Adaptation to use of antigen banks and emergency use
- Requirements for inactivation procedure added:
 - Linear log titre decrease
 - <1 infectious unit/10⁴ litres
- Details of in-process test for inactivation added
- Potency test unchanged

Phar Codex 7103/2003

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Why have both a guideline and a monograph?

- FMD vaccine is a special case
- No. of serotypes and no. of possible combinations makes strict compliance with directive and general monograph requirements impossible in many cases
- Guideline will give details of authorisation requirements not dealt with in monograph
- Guideline will explain in detail how the monograph provisions will be applied for marketing authorisation

Phar Codex 7103/2003

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2001 revision of monograph

- Initiated by input from FAO group with representatives of manufacturers
- Aimed at bringing monograph more into line with current practice
- Proposals to deal with GMP aspects in monograph
- Proposals used by Group 15V to develop 2001 revision proposal - but no GMP!
- Pragmatic approach to potency testing

Phar Codex 7103/2003

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2001 revision of monograph (2)

- Production section:
 - Formulation based on 146S antigen
 - Preparation in primary cells deleted
 - Limit of detection in inactivation test added
 - Batch potency test
- Safety test by recommended route
- Potency related to label claim
- Potency testing of single and combined antigens dealt with

Peer Code: 7103/2003

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2001 revision: critical issues

- Batch potency test:
 - cited as an example
 - 1 challenge test per antigen, 3 serological tests on challenge batch to define pass level
 - Role of reference sera
- Immunogenicity in ruminant species other than cattle and in non-ruminant species
- Definition of representative batch for emergency use
- Potency testing of pig vaccines

Peer Code: 7103/2003

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During revision

- European outbreak of FMD
- CVMP ad hoc group began work on guideline
- CVMP drafted detailed comments on revision proposal to “dovetail” guideline and monograph

Peer Code: 7103/2003

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During this conference

- An up-to-date account of control methods for FMD vaccine
- Role of vaccines in disease control
- Discussion of monograph revision proposals
- Discussion of the CVMP guideline

Peer Code: 17032003

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Office International des Épidémiologies
World Organisation for Animal Health
created in 1924 in Paris



**OIE Standards on
Foot and Mouth Disease**

Strasbourg (France), 17-18 March 2002

**Alejandro Schudel
OIE Scientific and Technical Department**

www.oie.int

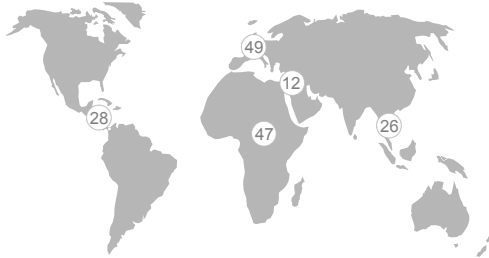


The OIE activities for the prevention and control of foot and mouth disease (FMD) are focused on the following four primary areas:

- ◆ Promoting transparency and knowledge of global animal disease status.
- ◆ Developing international standards that facilitate trade while minimising the risk of introducing FMD.
- ◆ Providing a declaration of freedom to countries or zones that meet the OIE Standards.
- ◆ Providing expertise and promoting international solidarity for the prevention, control and eradication of FMD.

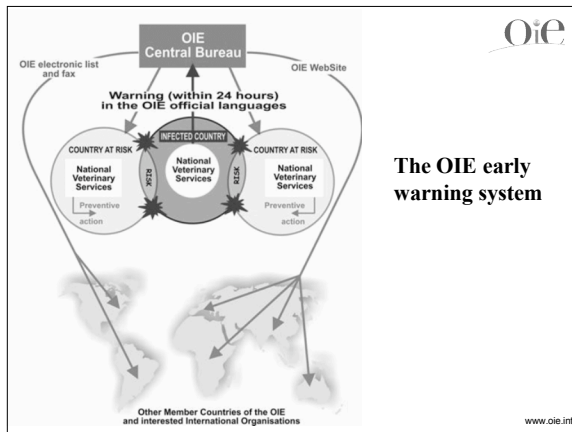
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OIE 162 Member Countries (May 2002)



Americas: 28 – Africa: 47 – Europe: 49 – Middle East: 12 – Asia: 26

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The OIE early warning system

www.oie.int

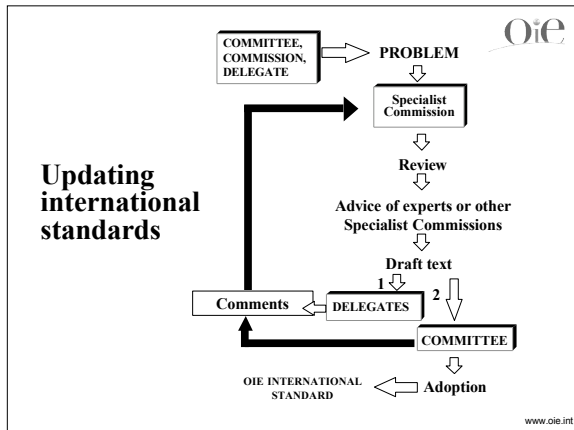
OIE International Standards



- ✦ International Animal Health Code - mammals, birds and bees
- ✦ International Aquatic Animal Health Code – fish, molluscs and crustaceans
- ✦ Manual of Standards for Diagnostic Tests and Vaccines
- ✦ Diagnostic Manual for Aquatic Animal Diseases
- ✦ Guidelines for the Surveillance of Animal Diseases

Also available on the OIE Website

www.oie.int



International Animal Health Code

FMD Chapter 2.1.1.

- Chapter 2.1.1 of the *Code* provides requirements that must be met for a country or zone to be defined as free of FMD and the recommendations regarding the safe import of animals or animal products into a country.
- This chapter deals not only with the occurrence of clinical signs caused by FMD virus (FMDV) but also with the presence of infection with FMDV in the absence of clinical signs. A definition for FMDV infection is provided.

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International Animal Health Code (contd)

♦ FMD free country without vaccination

- There has been no outbreak of FMD
- No evidence of FMDV infection
- No vaccination during the past 12 months
- Animals vaccinated against FMD have not been imported since the cessation of vaccination

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International Animal Health Code (contd)



✦ FMD free country with vaccination

- There have been no outbreaks of FMD for 2 years
- There has been no evidence of FMDV infection for 12 months
- Routine vaccination carried out for the purpose of the prevention of FMD and the vaccine used complies with the standards described in the *Manual*

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International Animal Health Code (contd)



✦ FMD free zone without vaccination

- There has been no outbreak of FMD, and
- No evidence of FMDV infection during the previous 12 months.
- There has been no vaccination during the last 12 months.
- The zone is surrounded by a surveillance zone or physical or geographical barriers.
- A country should describe in detail regulatory measures for the prevention and control of both FMD and FMDV infection and the system for preventing the entry of the virus into the FMD free zone.
- Animals vaccinated against FMD have not been introduced into the zone since the cessation of vaccination

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International Animal Health Code (contd)



✦ FMD free zone with vaccination

- There has been no outbreak during the last 2 years.
- The zone is surrounded by a buffer zone or physical or geographical barriers.
- The vaccine used should comply with the standards described in the *Manual*.
- A country should describe in detail regulatory measures for the prevention and control of both FMD and FMDV infection and the system for preventing the entry of the virus into the FMD free zone.
- Vaccination of zoo animals, animals belonging to rare species or breeds, or animals in research centres as a precaution for conservation purposes is an example of implementation of such a zone.

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International Animal Health Code (contd)



◆ Regaining FMD free status for a country or zone free without vaccination

Free status can be regained:

- 3 months after the last case where stamping out and serological surveillance are applied, or
- 3 months after the slaughter of the last vaccinated animal where emergency vaccination, stamping out and serological surveillance are applied, or
- 6 months after the last case or the last vaccination (according to the event that occurs the latest), where a stamping-out policy, emergency vaccination not followed by the slaughtering of all vaccinated animals, and serological surveillance are applied, provided that a serological survey based on the detection of antibodies to nonstructural proteins of FMDV demonstrates the absence of infection in the remaining vaccinated population.

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International Animal Health Code (contd)



◆ Regaining FMD free status for a country or zone free with vaccination

Free status can be regained:

- 6 months after the last case where a stamping-out policy, serological surveillance and emergency vaccination are applied, provided that a serological survey based on the detection of antibodies to nonstructural proteins of FMDV demonstrates the absence of infection, or
- 12 months after the last case where stamping out is applied if effective surveillance has been carried out.

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OIE Manual of Standards for Diagnostic Tests and Vaccines



- The *Manual* is a companion volume to the *Code* and provides a uniform approach to the diagnosis prevention and control of FMD.
- The purpose is to facilitate international trade in animals and animal products by describing internationally agreed upon laboratory methods for diagnosis and requirements for the production and control of FMD vaccines.
- The methods described also form the basis for effective FMD surveillance and monitoring.

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OIE Manual of Standards for Diagnostic Tests and Vaccines (contd)



- ✦ These include virus isolation and serologic techniques.
- ✦ The *Manual* provides a list of reference serums and prescribed tests; these are the serological tests that are required by the *International Animal Health Code* for the testing of animals in connection with international trade:
 - Virus neutralization (a),
 - The liquid phase blocking ELISA (b),
 - The solid phase blocking ELISA (c)and
The nonstructural protein test (NSP) 3ABC and EITB (d)

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OIE Manual of Standards for Diagnostic Tests and Vaccines (contd)



- ✦ NSP tests for FMD have an application in the identification of animals that have experienced virus replication. The basis of this test lies in the detection, in serum, of antibodies to the NSP's of FMD virus (FMDV). The detection of these antibodies is an indicator that viral replication, even if limited, has occurred and has been detected by the host immune system.
- ✦ A number of NSP's associated with FMDV replication have been identified and include: L, 3A, 3B, 2C, 3D, 3AB and 3ABC. These proteins have recently been used as antigens, either individually or in various combinations, in a number of ELISA and western blot techniques for the detection of antibody.

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OIE Manual of Standards for Diagnostic Tests and Vaccines (contd)



- ✦ An indirect ELISA and confirmatory Western Blot (EITB) are currently described in the *OIE Manual of Standards for Diagnostic Tests and Vaccines* (2000 edition), reviewed in 2002 and has been recently updated for the 2004 edition of the *Manual*.
- ✦ These tests are better indicators of previous infection in vaccinated animals compared with the currently available test methods.
- ✦ Current data would suggest that these tests are superior to virus isolation from OP secretions.
- ✦ It is not presently known how these tests would compare with genome detection in OP samples.

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OIE Manual of Standards for Diagnostic Tests and Vaccines (contd)



- ♦ The *Manual* establish that a reliable supply of pure, safe, potent, and effective vaccines is essential for maintenance of animal health and the successful operation of animal health programmes.
- ♦ Immunisation of animals with high quality vaccines is the primary means of control for many animal diseases. In other cases, vaccines are used in conjunction with national disease control or eradication programmes.

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OIE Manual of Standards for Diagnostic Tests and Vaccines (contd)



- ♦ Routine vaccination against FMD is used in many countries where the disease is endemic.
- ♦ Many disease-free countries maintain the option to vaccinate and have their own strategic reserves of highly concentrated inactivated virus preparations. Such antigen reserves offer the potential of supplying formulated vaccine in an 'emergency' at short notice.
- ♦ FMD vaccines are chemically inactivated cell-culture-derived preparations of the virus that have been blended with a suitable adjuvant.
- ♦ Because of the presence of multiple serotypes of the virus, many FMD vaccines are multivalent and it is common practice to prepare vaccines from two or more different virus strains.

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OIE Manual of Standards for Diagnostic Tests and Vaccines (contd)



Guidance on the requirements for FMD vaccines in the *Manual* are provided for:

Seed management

- a) Characteristics of the seed
- b) Method of culture
- c) Validation as a vaccine

Method of manufacture

In-process control

Batch control

- a) Sterility
- b) Safety
- c) Potency
- d) Duration of immunity
- e) Stability
- f) Preservatives
- g) Precautions (hazards)

Tests on the final product

- a) Safety
- b) Potency
- c) Purity

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OIE Manual of Standards for Diagnostic Tests and Vaccines (contd)



♦ In order to accompany the new standards approved for the FMD Code Chapter in May 2002, changes are being proposed for FMD vaccines requirements particularly in:

- **Methods of culture**, in order to remove the risk of contaminants
- **Potency**, 3 PD50/dose on Vaccines for routine prophylactic use, and 6 PD50/per dose on vaccines for "emergency vaccination"
- **Purity**, vaccinate (3 calves) three times during 3-6 months and then test the serum for antibodies to 3ABC/EITB.
- If the vaccine is being produced for a market where the NSP test will not be used, this NSP purity testing will not be required
- **Method of manufacture**: virulent FMD virus must be used to produce FMD vaccine, consequently the FMD vaccine production facility should have the appropriate biosecurity. The facility should meet the requirements outlined in Appendix 1.5.1 of the *Manual* for Containment Group 4 pathogens.

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• The Office International des Epizooties (OIE) has developed standards to reduce the risk of the spread of FMD through international trade. Standards developed by the OIE are recognised by the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) of the World Trade Organization (WTO).

• These standards include procedures for prompt reporting of FMD outbreaks; the development of standards that reduce the risk of the introduction of FMD; guidelines to certify FMD free countries and assistance to National Governments to develop FMD control programs.

• The goal of these standards is to facilitate trade while minimizing the risk of the introduction of FMD.

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World organisation for animal health

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**Viewpoint and Perspectives
of the FAO EUFMD
Research Group**

Kris De Clercq

United Nations

Food and Agriculture Organisation (FAO)

European Commission for the Control of
Foot-and-Mouth Disease (EUFMD)

The FAO EUFMD Research Group



Meeting RG 1997: The FMD Monograph

- Outdated: the use of tongue epithelium
- Inadequate procedures: virus inactivation
- Important items missing: vaccination of pigs
- Use of animals for control should be reduced

Critical changes to be made to the FMD Monograph

- 3Rs: *Replacement, Reduction, Refinement*
- Variability FMD virus
- Emergency vaccine
- Infected vs. vaccinated animals
- Structure of the Monograph

A proposal for revision of the FMD Monograph

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graph TD; A[ ] --> B["A proposal for revision of the FMD Monograph"]; B --> C["Group 15V of the Ph. Eur."]; B --> D["The CVMP/Immunologicals Working Party of EMEA"];
```

A strong reduction of the
in vivo tests
(Animal welfare)

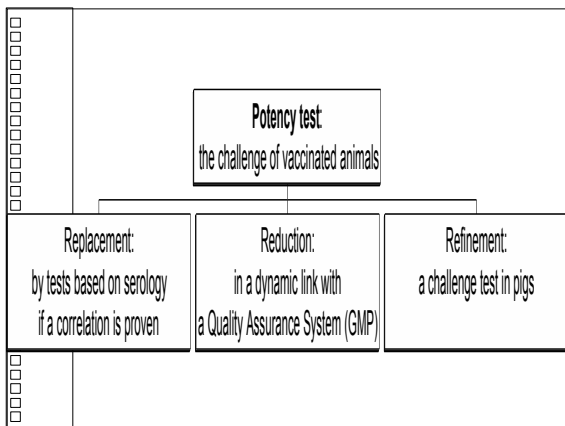
Safety test: detection of
residual infectivity

↓

Replacement by a sensitive cell
system with an internal validation:

- **Anderson et al. (1970)**
High sensitivity
Greater sample size
- **Gürhan (1998):**
in vivo: 252 vaccines / 1 failed
in vitro: 236 vaccines / 17 failed

+ An internal validation:
Cell sensitivity $\geq 10^6$ TCID₅₀ / μ g 146 S antigen



Alternative Potency test

- Pay and Hingley (1986): VNT
- Ahl et al. (1987): Plaque reduction test
- Hamblin et al. (1987): LPB ELISA
- Van Maanen and Terpstra (1988) :
VNT & LPB ELISA
Reproducibility evaluation
- Robilio et al. (1995):
LPB ELISA
435 vaccines
7390 vaccinated / challenged cattle
- Black et al. (1984): pigs
- Thevasagayam et al. (1997): overview

Criticism

- Ahl (1990) : different cell systems
- Lack of reference sera : project needed
- Validation of test (Jacobson, 1998)

Reduction of animals

- Financial implications
- Vaccine availability as tool for FMD control
- Global FMD eradication

Infected vs. vaccinated animals

- NSP test + highly purified vaccine
= System for CVOs
- Indirect test
- Validation on controlled vaccinated/infected animals
- Expensive

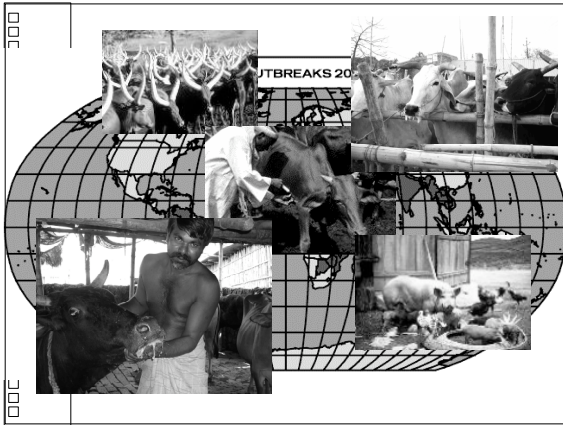
Variability FMD virus

- Emergency vaccine
- GMP + QA
- Broad + quick immunity
- Potency > 3 PD₅₀

1997 – 2003


- Revision FMD Monograph
- Position paper
- Good collaboration

**GLOBAL ERADICATION
OF FMD**




**When you consider a proposed
goal an illusion,
it tells me little about the reality
of that goal
but a lot about your will to
achieve it.**

(Peter van Straaten)


 European Commission
ENTREPRISE DIRECTORAT-GENERAL

Footh and Mouth Disease symposium
 EDQM, Strasbourg, 17-18 March 2003

**Regulatory Framework in EU for
 authorisation of FMD vaccines:
 Present and Future**


Anne GAUTRAIS-LE GOFF, DVM
 European Commission - Enterprise Directorate-General -
 Pharmaceuticals Unit (F2)

**Actual legal status of FMD
 Antigens/vaccines within EU**

- **Antigens:**
 - EU antigen bank : No authorisation in the framework of Directive 2001/82/EC but GMP and European Pharmacopoeia compliance.
 - National antigen banks: national authorisation
- **Vaccines:**
 - Vaccines issued from EU antigens bank have UK marketing authorisation
 - No community authorisation
 - National authorisation if national vaccines exist

2001 FMD Crisis in EU

- **General Public concern**
 - Animal welfare +++
 - Vaccination possibility +++
 - Public Health risks of the disease and of the vaccines available??

Changes in international animal health rules for trade

- May 2002
 - FMD chapter of the OIE Animal Health Code
- Emergency vaccination
 - a more attractive option in controlling FMD for Competent Authorities.

Specific challenges of FMD vaccination within EU

- **Prophylactic vaccination BANNED** since 1st January 1992 **in principle No FMD vaccine market except in case of emergency vaccination**
- Review proposal for **Emergency vaccination** as a primary response in the case of FMD outbreak **unpredictable FMD vaccine market** with specific constraints (stocks; authorisation procedure and requirements; time for release...)

EU legal framework on control measures for FMD

- **Revision of the legal framework of control measures for FMD (Dir. 85/511/EC and Dir 92/46/EC)**
- **Authorisation** of FMD vaccines
- **Section 8:** “Vaccination”
- **Section 14:** “Antigen and Vaccines Banks”

Present EU requirements

- **Directive 2001/82/EC**
 - Annex I -Title II
 - “Rules governing medicinal products in EU”
(Eudralex-volumes:6B, 7B)

- **CVMP Guidelines**

Present EU requirements

- **European Pharmacopoeia**
 - General Monograph
 - »“Vaccines for veterinary use”

 - Specific Monograph
 - »“Inactivated FMD vaccines for ruminants”

Directive 2001/82/EC

- Immunological Veterinary Medicinal Products (IVMPs) placed on the market within EU:
 - must be **AUTHORISED**

 - must fulfill the minimum requirements in terms of **Quality, Safety and Efficacy**

Directive 2001/82/EC

- Article 8:
 - “In **event of serious disease epidemic**, MS may provisionally allow the use of IVMPs without an authorisation for placing on the market, in the absence of a suitable medicinal product and after informing the Commission of the detailed conditions of use”

Future EU requirements

- **Full application of Directive 2001/82/EC**
 - in terms of **quality, safety and efficacy**
 - **CVMP Position paper on requirements for FMD vaccines** (*Out for consultation until 03/04/2003*)
- **Full application of Eur. Pharmacopoeia Monographs:**
 - Revision of the specific monograph
 - » **Inactivated FMD vaccines for ruminants**
 - Draft proposal of a specific monograph
 - » **FMD vaccines for pigs**

Future EU requirements

- **Full requirements** for authorisation of identified established vaccines strains, broadly protective for the EU livestock.
- **Specific requirements** for authorisation of identified NEW vaccine strains, urgently needed for the EU livestock.

I just want to be protected quickly by a safe
and efficacious vaccine!!!...
and stay alive for some years!!!