



# 'Authorisation of Vaccines - An example of evidence based medicine - past, present and future?'

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ASSURING THE SAFETY, QUALITY AND EFFICACY  
OF VETERINARY MEDICINES



- Evidence-based medicine (EBM) is the process of systematically reviewing, appraising and using clinical research findings to aid the delivery of optimum clinical care to patients. Rosenberg W, Donald A. (Evidence based medicine: An approach to clinical problem-solving. *BMJ* 1995; **310**:1122–1126.)
- External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision. (*BMJ* 312 : 71 (Published 13 January 1996) Editorial Evidence based medicine: what it is and what it isn't)



Evidence-based veterinary medicine is the use of best relevant **evidence**, in conjunction with clinical expertise, to make the best possible **decision** about a veterinary **patient**. In addition, the circumstances of each patient, and the circumstances and values of the owner/carer must also be considered when making an evidence-based decision.

(University of Nottingham, Centre for Evidence Based Veterinary Medicine)



# Why regulate medicines? (1)

- Salerno Medical Edict issued by Fredrick II of Sicily (1240), and ordered apothecaries to prepare remedies always in the same way – *forma curiae*.
- 1540 England manufacture of medicines subjected to under the Apothecaries Wares, Drugs and Stuffs Act.



# Why regulate medicines? (2)

- The first Pharmacopoeias in Europe date from the 16th century
- the first Spanish Pharmacopoeia was issued in 1581.
- England *The London Pharmacopoeia in 1618.*
- European Pharmacopoeia (EU member states plus others) 1964



# Why regulate medicines? (3)

Safety aspects incorporated during the early development of vaccines

- England, 1878, John Burdet-Sanderson and William Greenfield attenuated an anthrax strain by re-seeding the culture at 35°C strain without affecting its immunising potential.
- 1881, Louis Pasteur undertook a trial at Pouilly-le-Fort, near Paris where he compared the behaviour of vaccinated and unvaccinated sheep using a vaccine consisting of a culture attenuated by heating and containing an antiseptic known to inhibit the formation of spores. Unvaccinated animals died.
- 1882-1885 attenuation of rabies virus by passage through rabbits: Louis Pasteur and team. Used in human vaccination.
- In 1897, Albert Calmette and Camille Guérin took a bovine bacillus, isolated from the udder of a tuberculous cow, and passaged through glycerinated bile potato medium, resulting in an attenuated form – BCG used in 1921 in France in cattle and human vaccination against TB.



# Why regulate medicines? (4)

- 1937 over 100 people in the United States died of diethylene glycol poisoning
- following the use of a medicine which used the chemical as a solvent without any
- safety testing. This led to the Federal Food, Drug and Cosmetic Act with the premarket notification requirement for new drugs in 1938.
- 1955: "Cutter incident" with Salk Polio vaccine in the US: contamination of batches of inactivated vaccine with live virus: 40,000 children developed some form of disease, 56 seriously and 5 died.
- 1956-1960 Thalidomide first went on sale in Western Germany in 1956 was introduced in 46 different countries worldwide resulting in an estimated 10,000 babies being born with disability of varying severity. In the UK a Committee on the Safety of Drugs (CSD) was started in 1963 followed by a voluntary adverse drug reaction reporting system (Yellow Card Scheme) in 1964 This subsequently became the Committee on Safety of Medicines (CSM) under the terms of the Medicines Act of 1968, which provided the legal framework for the control of medicines in the UK.



# Why regulate medicines? (5)

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- 1965: first EEC legislation for medicine control
- **Medicines Act 1968** set requirements for pre authorisation data to support Q, S and E and set post authorisation requirements for adverse reaction reporting and ongoing manufacturing standards (GMP).



# Where we are today

- **1995: EU wide medicines legislation (directives)** set data requirements for placement of medicinal products on the market including those containing GMOs, responsibilities of manufacturers. Establishment of the European Medicines Agency (EMA) at Canary Wharf. EMA co-ordinates EU assessment of novel products including GMOs through the Committee for Veterinary Medicinal Products (CVMP)
- EU standards for Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Distribution Practice (GDP)
- **Review of EU legislation in 2001** leading to a new directive. This led to greater transparency (public reports on assessment) and availability (generics) and *revised data requirements*
- Implementation of 2001 in the UK through Vet. Med. Regs.



# Why regulate medicines? (5)

- bovine herpes virus 1 (BHV1) vaccine used in The Netherlands in 1999 that contained a small amount of bovine viral diarrhoea virus (BVDV1). Thousands of cows were vaccinated with BHV1 vaccine batches, and the question arose as to whether these small amounts of BVDV1, most likely not detected with in vitro tests, could have infected cattle
- FMD vaccines in Germany in the 70s



# Current framework

- Directive: lays out the legal framework of procedures, responsibilities of regulators and industry in placing a product on the market and maintaining a product on the market including the basic format of key product literature documents
- Technical annexes laying out the detailed requirements for data packages to support Marketing Authorisations . These are different for immunological products and pharmaceutical products



# Quality, safety and efficacy requirements

- *Quality:* Development pharmaceuticals; Consistency of production, Starting materials; manufacturing process and quality control; control of impurities/extraneous agents; inactivation validation; final product specification; stability.
- *Safety:* Target species; user; environment; consumer. Further requirements for live vaccines: spread, reversion, dissemination. Safety of proposed schedule.
- *Efficacy:* Claims and indications must be justified and supported by data. Field studies.
- Overall **Benefit/risk assessment** taking into account Q,S,E





quality

safety

efficacy



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Overall **Benefit/risk assessment**  
taking into account Q,S,E data

Reflected in terms of authorisation  
and product literature and leaflet

Summary of product characteristics



# What is an SPC

- **Gives product specific information to allow the product to be used safely and effectively.** *Package Leaflets and Labels are drawn up in accordance with the SPC.*
- **Every statement on an SPC is supported by data.** *The company use Q, S and E data to draft the SPC and the final version is an agreed document between company and regulator and forms part of the MA.*
- **Standard format and phraseology** *prescribed by the European medicines directive and EU guidelines.*
- **Publically available**

**SPCs of all UK authorised products can be found on VMD website [www.vmd.gov.uk/ProductInformationDatabase/](http://www.vmd.gov.uk/ProductInformationDatabase/)**



# Quality data and how these are reflected on an SPC

- *Quality:* Consistency of production, Starting materials; manufacturing process and quality control; control of impurities/extraneous agents; inactivation validation; final product specification; stability
- Many of the quality requirements form the “backbone” of the product to support consistent safety and efficacy of a product on a batch basis and do not form information relevant to the end user.



# Quality data and how these are reflected on an SPC

- What is in the product: how much of active ingredient/excipients/adjuvant: potency
- What it looks like and how it is presented
- How it should be stored
- How long it is stable for in the vial
- How long it is stable for once the vial has been opened



# Quality data and how these are reflected on an SPC

- Examples:
- Traces of antibiotics
- Potency
- In use stability – use immediately---  
use within 3-4 hours



# Safety requirements for live and inactivated vaccines

Studies to GLP

*Using*

Batches produced according to manufacturing process

*And of*

Maximum titre or *antigen content*

- By each recommended route of administration
- To each species and category intended for use
  - Most susceptible – seronegative
- At minimum age



# Safety requirements for live and inactivated vaccines

- Single dose
- *Overdose for live only (10x)*
- Repeat dose
- Reproductive safety
- Immunological functions
- Live vaccines: reversion to virulence (*5 passages*), spread, dissemination
- Residues
- Interactions
- Ecotoxicity assessment
- Field trials (*can use standard batches*)



# Safety

- The outcome of these studies set the warnings on the product literature for target animal, user and consumer. They must also support the safety of the whole vaccination schedule.
- E.g. if the vaccine contains an adjuvant there will be a warning for the user regarding self injection
- E.g. effects of vaccination such as lumps. Increase in temperature will be described so that the animal owner/vet know what are normal expectations



# Safety

- E.g.s do not use in pregnant animals – lack of reproductive safety – BLUETONGUE --- Exceptional circumstances – extract from EPAR
- E.g.s do not use across lay -----
- E.g.s minimum age --- tuberculin ----
- E.g.s special warnings re spread and humans handling vaccine—salmonella vaccines or improvac ----- EPAR



# Efficacy requirements for live and inactivated vaccines

- The outcome of these studies determines the claims made for the product on the product literature and also the authorised schedule
- E.g reduce excretion/viraemia



# Efficacy requirements for live and inactivated vaccines

Studies are not required to be run to GLP

*using*

Batches produced according to manufacturing process

**and**

Containing minimum titre or *antigen content*

*using*

recommended dose

*administered by*

Each recommended route *to* each category of each species



# Efficacy requirements for live and inactivated vaccines

- Onset and duration of protection must be established
- The influence of maternal antibodies should be investigated
- The efficacy of each component of a multi-valent product must be supported
- The efficacy of a “booster” dose must be supported



# Efficacy requirements for live and inactivated vaccines

- Any claim for concurrent or simultaneous administration with another vaccine must be addressed to show compatibility
- Field trials to address husbandry systems and breed differences



# Efficacy - modelling disease

- Some diseases with “straight forward” models e.g.
  - Rabies
  - Canine Distemper
  - Infectious Bursal Disease



# Efficacy - modelling disease

- Some diseases are less straight forward
- PMWS: circovirus: Model from E par ---- linking to field studies
- Mycoplasma in pigs: lab studies cannot monitor weight gain/loss /improvement
- Mastitis in cattle: hipra product E par--- field



# Efficacy modelling to support claims

- Bluetongue relevance of supported claim to field use:
- Epar for Intervet product: epediology models
- Salmonella claims and relevance to field



# Efficacy - SPC

Examples of claims:

Rabies ----protect claim? PhEur monograph requirements or dog vaccine claims

Bluetongue: reduce viraemia and example of data

Salmonella: reduce excretion– public health aspects



# Efficacy - SPC

- Examples of schedule modifications
- re maternal antibody warnings - dogs
- Cattle
- Lack of booster data



# Benefit/Risk

- Clinical benefit/risk assessment:  
which product  
cascade

use not in accordance with the SPC



# Benefit/Risk

- IBD
- Hot and non hot
- SPCs – clinical decision to use in particular circumstances



# Benefit/risk

- Dog vaccines-----longer D of Is to implement or not ?
- Clinical decision



# Post Marketing Surveillance

- SARRS
- Quality defects
- Suspension of an authorisation



# Has regulation improved medicines

- Contamination issues and new viruses:
  - S40 in cells
  - BVD from serum
  - TSE
  - retrovirus



Developing good regulation constant in reaction to new technology and to needs and feedback from the field – feedback mechanism

Use of products in the field --- clinical risk benefit as opposed to product risk benefit = vaccination GLS and post monitoring of products

(risk GLS management plans) and vaccination





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